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SIMMONDS' DISEASE (CACHEXIA HYPOPHYSEOPRIVA)

REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS AND A REVIEW OF THE LITERATURE

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Simmonds' disease may be defined as a clinical state, most common in women, characterized by progressive, extreme emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by a depression of the basal metabolic rate. Untreated, it is a progressively fatal disease, usually terminating suddenly with a short period of coma. There are often mental disturbances closely simulating Korsakoff's syndrome, so that the patients are sometimes first seen by the psychiatrist. The pathologic basis for the condition is varied. In general, it may be said that any process that destroys the anterior lobe of the pituitary gland may give rise to the clinical picture. A "splanchnomicria," an abnormal smallness of the viscera, is the only constant postmortem observation aside from changes in the pituitary body. This was first pointed out by Simmonds.[1]

Some idea of the various concepts of the fundamental nature of the disease can be obtained from the names that have been applied to it by different authors. Simmonds [1] called it "cachexia with fatal termination." Lichtwitz,[2] who did not believe that cachexia was an essential part of the clinical picture, called it Simmonds' disease. Colden [3] would name it "dystrophia cachecto genitalis" to indicate its relation to the syndrome of Fröhlich, apparently unaware that Zondek [4] had already

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The case to be reported was observed in 1929, and the manuscript was prepared in 1930. Publication was unavoidably delayed until this time.

1. Simmonds, M.: Deutsche med. Wchnschr. **40**:322, 1914.

2. Lichtwitz, L.: Klin. Wchnschr. **1**:1877, 1922.

3. Colden, C.: Monatsbl. f. Augenh. **82**:769, 1929.

4. Zondek, H.: Ztschr. f. klin. Med. **99**:147, 1924

used that term. Urechia [5] suggested "cachexie tuberienne" to show that the region of the tuber cinereum, rather than the hypophysis, is primarily involved. Finally, Bauer [6] combined all the prevailing notions in the term "hypophysare-nervöse kachexie."

It is obvious that the clinical picture existed before 1914, when it was first described by Simmonds. However, it does not seem that any of the earlier writers, Wagner,[7] Formanek,[8] Marburg [9] or Falta,[10] realized that a distinct clinical picture was associated with atrophy of the pituitary gland and was secondary to this pituitary change. Virchow,[11] who saw a case of pituitary gumma, did not record any typical findings. Goetsch,[12] in 1914, did not describe a clinical state associated with pituitary atrophy.

The disease has been almost completely ignored in the American literature. It is not even mentioned in the reviews of Abrahamson,[13] Englebach,[14] Tierney,[15] Frazier,[16] Eidelsberg [17] or Rowe and Lawrence.[18] The latter, with an unusually large series of over four hundred selected pituitary cases, did not record one of cachexia. They stated, "under weight was found chiefly in adolescents showing the Levi-Lorain type of disturbance and seldom amounted to more than 20%, the maximum recorded being 30%." The report of Good and Newman [19] is the only case recorded in the English literature.

There is no doubt that destruction of the parenchyma of the anterior lobe of the pituitary gland may produce the clinical picture that goes by the name of Simmonds' disease. It is my plan to review the recorded cases, add a case of my own and to indicate the basis on which the condition may be recognized intra vitam.

5. Urechia, C. J., and Elekes, N.: Encéphale **21**:352, 1925.

6. Bauer, Julius: Innere Sekretion, Berlin, Julius Springer, 1927.

7. Wagner: Arch. f. Heilkund. **3**:381, 1862 (not seen in original).

8. Formanek, F.: Wien. klin. Wchnschr. **22**:603, 1909.

9. Marburg: Ztschr. f. Nervenh. **36**:116, 1909.

10. Falta, Wilhelm: Die Erkrankungen der Blutdrüsen, Berlin, Julius Springer, 1913.

11. Virchow: Virchows Arch. f. path. Anat. **15**:299, 1858.

12. Goetsch, E.: Quart. J. Med. **7**:173, 1914.

13. Abrahamson, Isador, and Cleimenko, Hyman: A Study of One Hundred Selected Cases of Pituitary Disease, J. A. M. A. **69**:281 (July 28) 1917.

14. Englebach, W.: Endocrinology **4**:347, 1920.

15. Tierney, J. L.: Endocrinology **7**:536, 1923.

16. Frazier, C. H., and Grant, F. C.: Pituitary Disorder, J. A. M. A. **85**:1103 (Oct. 10) 1925.

17. Eidelsberg, Joseph: Hypopituitarism, J. A. M. A. **89**:449 (Aug. 6) 1927.

18. Rowe, A. W., and Lawrence, C. H.: Endocrinology **12**:245, 1928.

19. Good, T. S., and Newman, K. O.: Lancet **1**:765 (April 13) 1929.

Credit for the first clinical diagnosis of pituitary cachexia belongs to Nonne,[20] who, knowing of Simmonds' reports, recognized a case in 1919. The diagnosis in this case was later confirmed by Simmonds at autopsy.

REPORT OF A CASE

Clinical History.—A Hungarian housewife, aged 53, had lived in New York for the past thirty-seven years. Her father and mother had died at advanced ages of unknown causes. She knew of no illness resembling her own that had occurred in her family. In her infancy she suffered from an attack of "smallpox." Her menses began at 14 and were regular until the onset of her present illness. She married at 20 and was pregnant eight times. Three children were well; two died

Figure 1

Figure 2

Fig. 1.—The patient at 18 years of age.

Fig. 2.—The patient at 30 years; emaciation is just indicated.

in infancy, and three pregnancies terminated in abortions. No information regarding the nature of the deliveries could be obtained.

At 40, shortly after the birth of her last child, the patient's menses ceased. She noticed that she tired easily and could no longer do her usual household work. At that time she weighed 130 pounds (59 Kg.) and showed no evidences of any illness.

For the last twelve years of her life she had become progressively weaker and more cachectic. This change had been most accentuated in the past eighteen months. At the time of examination the patient weighed only 60 pounds (27.2 Kg.),

20. Nonne and Bostroem: Deutsche med. Wchnschr. **44**:871, 1919.

a loss of 53 per cent of her former body weight. Her teeth had become carious, and most of them had fallen out. Menses and libido had been absent since her fortieth year. Emaciation had been progressive and marked, and it was believed that the patient was suffering from a latent carcinoma.

Three weeks before admission she suffered from an attack of abdominal cramps and diarrhea which yielded to the usual therapy. Blood was never noted in the stool. This diarrhea had not returned, but the patient had a moderate anorexia.

Examination.—Physical examination revealed an extremely cachectic woman who had lost practically all her subcutaneous fat. The cachexia was as extreme as one sees in the most advanced cases of carcinomatosis or tuberculosis. Literally, the patient presented "nothing but skin and bones." The skin was of a sallow, yellow hue, but there was no icterus. The facial skin was wrinkled. The eye-

Fig. 3.—The patient at 51; cachexia is obvious.

brows were sparse, especially at the outer margin. The eyes were sunken and the conjunctivae pale. The fundus showed atherosclerotic vessels, but no other changes. The patient was almost edentulous, and the few remaining teeth were very carious. There was no pigmentation of the mucous membranes. The thyroid could not be felt. The breasts were very atrophic. No abnormal findings were noted in the thorax. No abdominal viscera could be felt through the extremely thin abdominal wall. The wasting was very marked in the extremities, and there was a slight grade of pretibial edema (nutritional?). There were no positive neurologic findings. The pubic hair was very sparse, as was the hair in the axillae. The genitalia were atrophic.

The blood pressure was 120 systolic and 80 diastolic; the hemoglobin, 47 per cent, and the color index, 0.9. The leukocytes numbered 6,400, of which 60 per cent were polymorphonuclears, 30 per cent lymphocytes, 7 per cent monocytes, 1 per cent myelocytes, and 1 per cent lymphoblasts. The von Pirquet test gave

negative results. The stool was normal and contained no blood. A gastric test meal revealed complete achlorhydria even after 0.5 mg. of histamine subcutaneously, but ferments were present. There was no polyuria, and the specific gravity averaged 1.016. The urine was normal. The blood sugar was 90 mg. per hundred cubic centimeters, and the urea nitrogen, 14 mg. The basal metabolic rate was minus 10 per cent. X-ray pictures of the sella turcica, stomach and chest revealed no abnormalities.

Although the case had been referred with the suggestion that the patient was suffering from an intra-abdominal neoplasm, at no time was the admission diagnosis of cachexia of hypophyseal origin doubted. The extreme emaciation, repeated pregnancies, early loss of menses, sallow, wrinkled skin, genital atrophy and loss of pubic and axillary hair gave indications that the cachexia was not of the usual variety. The patient died suddenly several days after admission.

Fig. 4.—One week before death; cachexia is extreme.

Pathologic Data.—Autopsy was performed twenty-four hours after death. The body was that of an elderly woman, extremely undernourished. There was no jaundice. There was some edema of the legs.

The panniculus adiposus was entirely absent. There was a small amount of ascites. The peritoneal surfaces of the abdomen were everywhere smooth and normal.

The heart was very small, weighing only 170 Gm. The pericardium was normal. The valves and chambers were normal. The coronary arteries were tortuous and showed moderate sclerosis. The aorta was normal.

There was moderate bilateral emphysema. The upper portion of the lower lobe of the right lung showed a calcified primary infection situated subpleurally. The right lung weighed 425 Gm., and the left lung, 340 Gm. There was a moderate grade of pulmonary edema.

The liver weighed 895 Gm. The capsule was smooth. On cut section, the architecture of the liver was poorly visualized. The gallbladder and ducts were normal.

The spleen weighed only 70 Gm.; otherwise, it was normal.

The kidneys were small and firm and weighed 100 Gm. each. The capsule stripped with difficulty, numerous gray areas about 0.5 by 0.25 cm. in the rough surface being uncovered. The cortex and medulla were injected. The pelves, ureters and bladder were normal.

There was some slight ulcerations in the lower third of the esophagus. There was an hour-glass constriction in the distal third of the stomach, which showed no ulcerations. In the small intestine there were numerous superficial small ulcera-

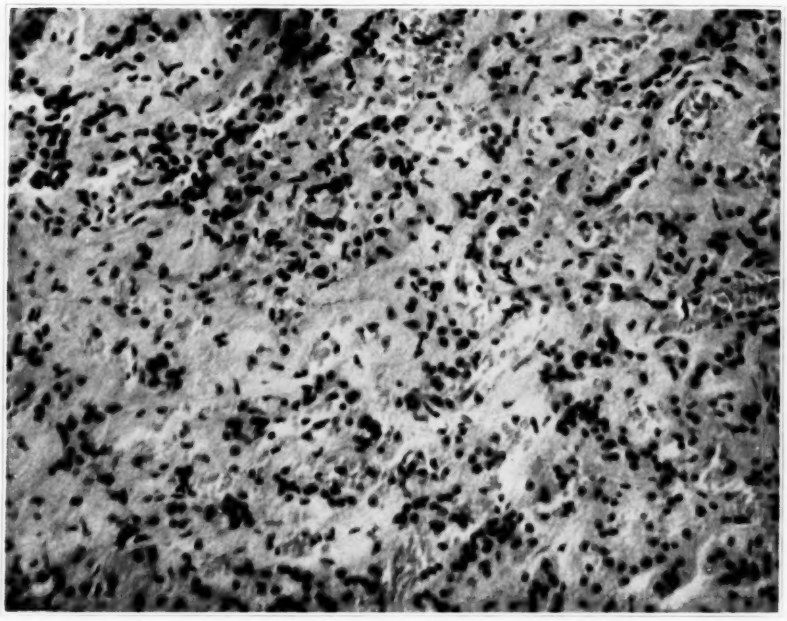

Fig. 5.—Section of the anterior lobe of the pituitary, showing the marked increase in interstitial tissue and the reduction in parenchyma.

tions, some as large as a small pea. No evidences of these ulcers could be seen on the serosa. The large intestine was normal.

The uterus was senile. The ovaries were small.

The pancreas weighed 70 Gm.

The suprarenal glands weighed 15 Gm. each. The cortex was very thin.

The thyroid was normal on section.

Microscopic Data.—There was marked atrophy of the heart, with pigmentation.

Peripheral fatty infiltration of the liver was present. The cells about the central vein showed a great amount of pigment. Brown atrophy was present.

There were small areas of fibrosis and moderate arteriosclerosis of the kidneys.

Atrophy of the acini of the pancreas was evident.

The thyroid was atrophied.

There was atrophy of the medulla of the suprarenals.

There were superficial ulcerations of the mucosa of the intestines, with an inflammatory reaction.

Conclusions (Dr. Klemperer).—"A case of extreme cachexia in a woman of 53 years. Autopsy and examination of the internal organs did not reveal anything but an extreme atrophy. The glands of internal secretion were not involved in any *sclerotic* process. The only positive findings were the marked hyperplastic

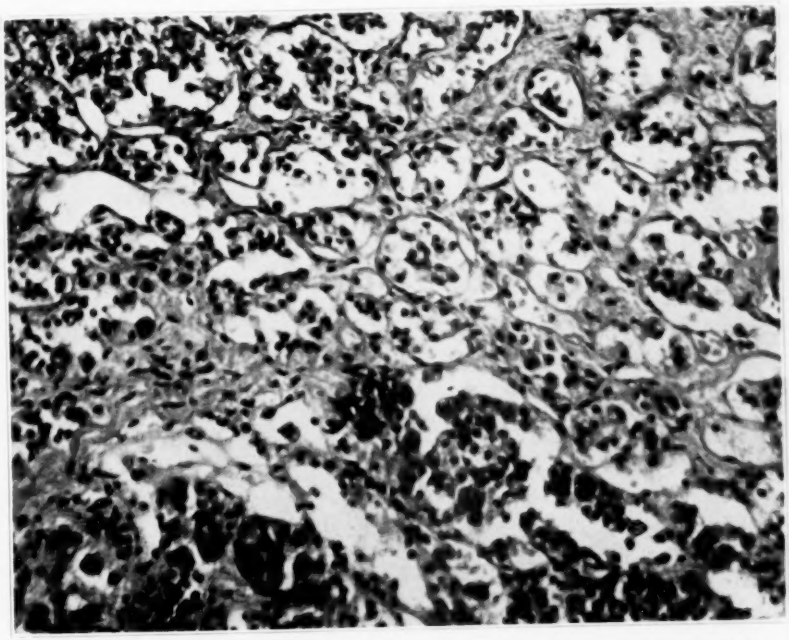

Fig. 6.—Section of the anterior lobe of the pituitary, showing advanced disintegration of the parenchyma.

gastritis and the superficial catarrhal ulcers of the small intestines. From these findings an explanation as to the cause of the cachexia cannot be given."

The brain was examined by Dr. J. H. Globus, and the following is his report of the positive findings: "The pituitary body was smaller than normal. Microscopically it showed marked alterations in its anterior lobe. There was extensive fibrosis and marked reduction in the parenchymatous elements. The latter showed advanced degeneration as evidenced by shrinkage and desquamation of cells and pyknosis of the nuclei.

"The histologic appearance of this organ was in full accord with that described in Simmonds' disease.

"The hypothalamic region revealed no definite pathologic alteration."

SUMMARY OF REPORTED CASES

At this point I wish to add a few notes regarding cases that either have been published as Simmonds' disease or have been quoted by writers other than the original authors as such. They are added for the sake of completeness with a word of criticism.

The case of Josephy [21] is not to be considered as one of Simmonds' disease because the clinical picture is insufficient and the loss of weight occurred just ante mortem.

The case of Hirsch [22] has been quoted as one of pituitary cachexia, but as the patient had a carcinoma of the esophagus with extensive metastases, one need not implicate the pituitary in the causation of the cachexia, although the gland showed some changes.

The case of Knoll [23] cannot be accepted as a proved case. There was no cachexia, and the postmortem examination was limited to the head. There is every reason to believe that the patient suffered from a full blown, active, miliary tuberculosis and that the destruction of the pituitary was only one manifestation of this generalized process.

The case of Lindemann [24] has been quoted as a case of Simmonds' disease, although the author expressly favored a diagnosis of pluriglandular sclerosis. In addition, there was no cachexia, and there seems to be no reason to include the case with those of pituitary disease.

The second case of Jakob [25] can scarcely be recognized as a case of Simmonds' disease because there was a fresh tuberculous meningitis. However, the hypothermia, bradycardia, achylia, mental changes and loss of pubic and axillary hair suggest some pituitary disturbance.

The case of Worms and Delater [26] cannot be accepted as a report of Simmonds' disease, although it has been so presented by others. The authors state distinctly that no pituitary symptoms were present, and that the testes were normal. This case is best considered as one of the group that shows no characteristic clinical picture in spite of complete pituitary destruction.

The interesting case of Pribram [27] is difficult to classify exactly. At 31 the patient had a difficult labor after which she "aged 20 years in two weeks." Later she lost all her teeth, became amenorrheic, lost her eyebrows, axillary and pubic hair and suffered from a complete loss of libido. The patient had episodes of "hibernation" from which she could be aroused by thyroid extract. She died at 50 years of age. Postmortem

21. Josephy, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **58**:56, 1920.
22. Hirsch, O.: Deutsches Arch. f. klin. Med. **140**:323, 1920.
23. Knoll, W.: Wien. Arch. f. inn. Med. **4**:555, 1922.
24. Lindemann: Virchows Arch. f. path. Anat. **240**:11, 1923.
25. Jakob, A.: Virchows Arch. f. path. Anat. **246**:151, 1923.
26. Worms, G., and Delater, G.: Rev. neurol. **2**:361, 1925.
27. Pribram, E. O.: Virchows Arch. f. path. Anat. **264**:498, 1927.

examination revealed an advanced hypophysitis and thyroiditis of unclear etiology, probably secondary to some form of sepsis. It seems likely that many of the symptoms were due to an insufficiency of the anterior pituitary lobe. This is apparently the same case that Pribram reported in 1922 and is abstracted here as case 12 (table 1).

The case of Van Bogaert [28] cannot be considered one of Simmonds' disease. The patient suffered from dystrophia adiposogenitalis (Frohlich) and lost weight only terminally. In addition, the anterior pituitary lobe was quite normal. In this case the tumor was suprasellar, and it is interesting to note that hypothermia and a lowered basal metabolic rate were present possibly as indications of symptoms in the midbrain secondary to the primary focus.

The case of Frazier [29] cannot be accepted. The patient was a boy, the clinical picture was not definite, and a complicating syphilis was probably present. In addition, a postmortem examination was not performed and for reasons noted this alone would exclude the case.

The following four authors have presented cases without anatomic confirmation as Simmonds' disease. None of them, however, seems to have a case that is to be accepted without doubt.

It does not seem to me that Lichtwitz has enough evidence to consider the three cases that he presents as clinically likely examples of Simmonds' disease.

Although Schneider [30] considered the cachexia in his case of hypophyseal origin, it seems best to attribute the lack of development and stigmas of infantilism to the extensive tuberculosis from which the patient suffered rather than to a primary pituitary lesion.

The case of Korovnikov and Beresniak [31] does not seem to have enough features of Simmonds' disease to warrant including it as a likely case.

One can scarcely accept the case of de Rudder.[32] In spite of the depression of the basal metabolic rate and extreme cachexia (the 9 year old patient presented the weight of a 1½ year old infant), there are not enough characteristics to be certain that a marked abiotrophy of the central nervous system was not present rather than a specific hypophyseal disorder.

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28. Van Bogaert, Ludo: The Thalamic and Parkinsonian Types of Infundibular Tumors, Arch. Neurol. & Psychiat. **19**:377 (March) 1928.

29. Frazier, C. H.: Pituitary Cachexia, Arch. Neurol. & Psychiat. **21**:1 (Jan.) 1929.

30. Schneider: Wien. klin. Wchnschr. **35**:233, 1922.

31. Korovnikov, A., and Beresniak, M. E.: Klin. med. **6**:539, 1928.

32. de Rudder, B.: Ztschr. f. Kinderh. **50**:113, 1930.

TABLE 1.—*Cases Confirmed by Postmortem Examination; Symptomatology and Physical Findings*

Case	Author	Sex	Age	Type of Onset	Duration in Years	Cachexia	Asthenia	Premature Aging	Age at Menopause	Number of Pregnancies	Genital Atrophy (Male)	Loss of Libido	Loss of Pubic Hair	Loss of Axillary Hair	Atrophy of Jaw	Loss of Teeth	Hypotension	Hypothermia	Eosinophilia, per Cent	Anemia	Additional Findings
1	Simmonds [1]	F	46	Unknown	Unknown?	+	..	+	..	..	..	..	+	+	..	..	..	..	..	..	
2	Maresch [24]	F	33	After birth of twins	11	+	..	..	29	..	..	..	+	..	..	+	..	+	2.4	..	Bradycardia
3	Simmonds [33a]	M	58	Gradual with asthenia	2	+	+	..	..	..	..	..	+	+	..	..	..	..	5	..	
4	Simmonds [33a]	F	9	Gradual with asthenia	1	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	
5	Fraenkel, E.: Deutsche med. Wchnschr. **43**: 1569, 1916; Neurol. Centralbl. **35**: 778, 1916	F	45	After pregnancy	9	+	+	+	36	11	..	..	+	..	..	..	..	..	..	60%	Polyuria
6	Schlagenhafer [52]	F	27	Gradual with asthenia	1	+	+	..	26	..	..	..	..	..	..	..	..	..	..	..	
7	Simmonds [33b]	F	48	After pregnancy	18	+	+	..	30	..	..	..	..	..	..	..	..	..	..	..	
8	Simmonds [33b]	F	35	No history	Unknown	+	..	+	..	..	..	..	+	+	+	+	..	..	..	44%	Hypoglycemia
9	Fahr,[38] Reiche [41]	F	50	Became weak after febrile illness at 24	26	moderate	+	..	24	..	..	..	+	+	+	+	..	+	17 to 22	..	Anacidity; pigmentation of skin
10	Schaefer [57]	F	22	After rheumatic fever at 21	1	+	..	..	21	..	..	..	+	+	..	..	..	..	..	..	Sudden death
11	Budde, M.: Frankfurt. Ztschr. f. Path. **25**: 16, 1921	F	27	Gradual	..	+	..	+	..	.	..	..	+	+	..	..	..	..	..	..	
12	Pribram, B. O.: Verhandl. d. deutsch. Kong. f. inn. Med. **34**: 355, 1922	F	32	Sudden after manual removal of placenta	..	+	..	..	..	7	..	..	+	..	+	..	..	+	..	..	
13	von Monakow [34]	M	60		..	+	+	..	..	..	+	..	+	+	..	..	..	..	..	..	
14	Jaffe [58]	M	33	Gradual	7 mo.	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
15	Simons [35]	F	42	Gradual	8	+	..	+	34	..	..	..	..	..	+	+	..	..	..	..	Lost 63% of body weight
16	Keilmann [37]	F	20	After puerperal signs	4	+	+	..	16	..	..	..	+	+	..	..	..	..	..	+	Polyuria
17	Hochstetter and Veit [60]	M	34	Gradual with headache and loss of libido	4	+	+	..	..	..	+	+	+	+	+	+	+	..	..	..	Osteoporosis of skull
18	Colden [3]	M	44	With psychosis called Korsakoff	..	+	+	..	..	..	+	..	+	+	..	..	..	..	..	..	Polyuria
19	Gralse [40]	F	40	Sudden after pregnancy	3	+	+	+	34	8	..	..	+	+	+	+	..	+34°	11	..	
20	Jakob, A.: Deutsche med. Wchnschr. **49**: 735, 1923	F	40	After pregnancy	5	+	+	+	35	7	..	..	+	+	..	..	..	+	..	..	

21	Buday [59]	F	7	Anemia and weakness after postpartum sepsis	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..		
22	Jakob [25]	F	42	With mental symptoms	3	+	+	+	36	9	..	..	+	+	..	..	..	+34.1°	..	..		
23	Reinhardt [55]	M	..	After fracture of skull	Several yrs.	+	+	..	..	..	+	+	+	+	+	+	..	..	..	..		
24	Müller: Klin. Wchnschr. **2**: 1576, 1923	F	59	Died of cerebral hemorrhage	7	+	..	..	..	..	..	..	+	+	..	..	..	..	..	..	No eyebrows or eyelashes	
25	Hirsch and Berberich [70]	F	57	Gradual	17	+	..	..	52	..	..	+	+	+	..	+	..	..	..	..	Questionable case: polydypsia, pigmentation	
26	Kiyono [63]	M	36	With loss of libido	1	+	..	..	..	..	+	+	+	+	..	..	..	..	..	..		
27	Lang [30]	F	38	Headache and Korsakoff syndrome	2	+	..	..	..	..	..	..	+	+	..	..	..	..	..	..		
28	Graubner, W.: Ztschr. f. klin. Med. **101**: 249, 1925	F	52	After pregnancy with eclampsia	20	+	+	+	..	5	..	..	+	+	+	+	..	..	..	+	Syphilis at 23; ascites, 119 liters removed; no eyebrows	
29	Shereshevsky [50]	M	28	After fall from horse	19 mo.	+	+	..	..	..	+	+	+	+	..	..	+	+	..	..	After injury of skull; bradycardia	
30	Tauber, R. L.: Med. Klin. **23**: 1429, 1927	F	38	After pregnancy	4	+	..	..	..	..	..	..	+	+	..	..	..	..	..	..		
31	Reiche [42]	F	67	Weakness	1	+	..	..	..	2	..	..	+	+	+	+	..	+	7	..	No eyebrows or eyelashes; sella normal	
32	Pennetti [62]	F	54	Progressive asthenia	10	+	+	+	47	5	..	..	+	+	..	..	..	..	..	..		
33	Mogilnitzky [61]	M	15		..	+	..	+	..	..	..	..	+	+	..	+	+	..	..	..		
34	Thür: Frankfurt. Ztschr. f. Path. **36**: 603, 1928	F	37	After pregnancy with hemorrhage	2	+	+	..	..	4	..	..	+	+	..	..	..	..	..	..	Polydipsia: sudden death; no eyelashes or eyebrows	
35	Meng [74]	F	69	After pneumonia	20	+	+	..	..	..	..	..	+	+	+	+	..	..	..	..		
36	Knauer: Centralbl. f. allg. Path. u. path. Anat. **42**: 1, 1928	F	42	After pregnancy with hemorrhage	4	+	+	..	..	4	..	..	+	+	..	..	..	..	..	..		
37	Altmann [75]	F	48	Progressive cachexia	11	+	+	..	43	2	..	..	+	+	..	..	..	+	..	+	Basal metabolic rate −18%	
38	Good and Newman [19]	F	37	Rapid cachexia	1	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..		
39	Omelskyj, E.: Virchows Arch. f. path. Anat. **271**: 377, 1929	F	58	After delivery of 4th child at 34	24	+	+	..	34	4	..	..	+	+	..	+	..	..	..	..	No eyebrows	
40	Reiche [26]	F	65	After complicated delivery	44	+	+	..	21	..	..	..	+	+	..	+	..	..	..	..	Cholesterol 360 mg.	
41	Merz, W.: Frankfurt. Ztschr. f. Path. **40**: 452, 1930	M	37	After sore throat	20	+	+	..	..	..	..	..	+	+	..	..	..	..	8.6	..	Basal metabolic rate −35%	

TABLE 2.—*Pathologic Findings*

Case	Weight of Gland, Gm.	Anterior Lobe	Posterior Lobe	Atrophy of Other Endocrine Glands	Splanchnomieria	Comment
1	0.3	Extreme atrophy; only few cell islands	Small	.....	..	
2	Small	Small, with atrophic changes	Practically normal	Thyroid and suprarenals	..	Sella small; gland 10 by 8 by 3 mm.
3	.....	Complete destruction by basophilic adenoma	Same as anterior	.....	..	
4	.....	Complete destruction by basophilic adenoma	Same as anterior	.....	..	
5	0.15	Completely replaced by fibrous tissue	Normal	.....	..	
6	.....	Complete destruction by tuberculous caseation	Same as anterior	.....	..	
7	0.225	Completely replaced by fibrous tissue; only few cell nests seen	Normal	.....	+	
8	0.200	Fibrosis with few cell nests	Normal	Normal	+	
9	.....	Replaced by connective tissue mass	Normal	.....	+	
10	. . .	Multiple areas of necrosis	Same as anterior	.....	..	"Either syphilis or tuberculosis"
11	.....	Destroyed by carcinoma	Same as anterior	.....	..	Primary, unknown
12	....	Atrophic and sclerotic	Normal	Thyroid	..	
13	.....	Destroyed by an "inflammatory process"	Normal	Testes	..	
14	....	Syphilitic leptomeningitis with gumma of stalk and infundibulum	Normal	.....	–	
15	0.4	Atrophic (no microscopic study)	Atrophic	Normal	..	
16	.....	Cyst weighing 93 Gm. completely destroying anterior lobe	Normal	.....	..	
17	0.5	Extreme degeneration with fibrosis	Normal	Thyroid, suprarenals, testes, parathyroids	..	
18	. . .	"Squamous-epithelio-cysto-papilloma" of processus lingualis of anterior lobe; some normal tissue	Normal	.....	–	
19	0.4	Atrophic	Normal	Suprarenals and thyroid	..	
20	0.58	Atrophic	Normal	Thyroid and suprarenals	..	
21	.....	Gumma of pituitary...	.....	.....	–	
22	0.4	Completely replaced by fibrous tissue	Some glial reaction	.....	..	Probably secondary to embolus
23	....	Destroyed by hematoma	Destroyed	.....	..	After fracture of skull
24	0.13	Only few cells could be found	Normal	Thyroid	..	
25	0.60	Homogeneous mass with cholesterol crystals and fibrosis; few cell nests	Same as anterior lobe	.....	..	
26	....	Cysts with considerable destruction	Normal	Testes; prostate	..	
27	.....	"Squamous cell cyst papilloma"	Normal	.....	–	
28	Small	Cells small and atrophic	Normal	.	..	No cause for ascites
29	....	Advanced atrophy	Normal	.....	..	
30	0.28	Very atrophic and fibrotic; cells could scarcely be recognized	.....	Thyroid, suprarenals, ovaries	..	Secondary to emboli

TABLE 2.—*Pathologic Findings—Continued*

Case	Weight of Gland, Gm.	Anterior Lobe	Posterior Lobe	Atrophy of Other Endocrine Glands	Splanchnomicria	Comment
31	.....	Extreme atrophy; cells could scarcely be recognized	Normal	.....	..	Syphilitic aortitis
32	.....	"Fibroblastic endothelioma of Masson" with pressure atrophy of entire gland	Same as anterior lobe	.....	..	
33	.....	Carcinoma of pituitary with destruction	Same as anterior lobe	Testes	+	
34	3 mm. in diameter	Only occasional microscopic nest could be found	Same as anterior lobe	Thyroid	+	
35	0.35	Could hardly be found	Pseudoadenoma formation	Thyroid, suprarenal	+	
36	0.37	More than half replaced by fibrous tissue	Normal	.....	..	Some tuberculosis of pleura and peritoneum
37	0.28	Extreme atrophy	Normal	.....	..	
38	Small	Small and fibrotic with only an occasional nest of basophilic cells remaining	Normal	.....	..	
39	9.32	Extremely small; atrophy with fibrous replacement	Normal	Suprerenals, thyroid	..	Probably embolic
40	.....	Only a tiny residue could be found; some calcification	Normal	.....	..	
41	.....	Cyst with pressure ...	Normal	.....	+	

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis.—The essential features of the syndrome were detailed by Simmonds in his three publications,[33] in which he reported cases of the disease. Since then, other observers have added significant findings so that now there is a distinct and readily recognizable clinical picture that goes by the name of Simmonds' disease.

Women are more susceptible to the disease than men. In fact, only ten proved cases have been reported affecting the male sex. The fourth, fifth and sixth decades are most frequently affected, although cases have been reported as early as the ninth and as late as the sixty-ninth year.

The onset is usually insidious and often follows a complicated labor. It has been noted in women who have had a large number of children, especially if in rapid succession. It has been suggested that a functional exhaustion of the pituitary may be the result of this repeated child bearing.[34] The disease is progressive and, untreated, the patients all die as a result of intercurrent infection or in a short period of coma.

The cachexia is extreme and exceeds that found in any other condition. It is usually the outstanding part of the clinical picture, but cases have been reported in which the loss of weight was only slight.

33. Simmonds, M.: (*a*) Deutsche med. Wchnschr. **42**:190, 1916. (*b*) ibid. **44**:852, 1918. (*c*) Bostroem, A.: ibid. **44**:871, 1918; (*d*) Med. Klin. **14**:690, 1918.

34. Maresch: Verhandl. d. deutsch. path. Gesellsch. **17**:212, 1914.

TABLE 3.—*Clinical Cases; Symptomatology and Physical Findings* *

Case	Author	Age	Type of Onset	Duration in Years	Cachexia	Asthenia	Premature Aging	Age at Menopause	Number of Pregnancies	Genital Atrophy (Male)	Loss of Libido	Loss of Pubic Hair	Loss of Axillary Hair	Atrophy of Jaw	Loss of Teeth	Hypotension	Hypothermia	Eosinophilia, per Cent	Anemia	Additional Findings
1	Simmonds [1]	46	After puerperal sepsis	10	+	+	+	..	5	..	..	..	..	+	+	..	..	..	..	
2	Cyran [51]	48	After fracture of skull	Indefinite	+	..	..	..	..	..	..	..	..	+	+	..	..	..	..	
3	Reye: Med. Klin. **16**: 1313, 1920	50	Gradual	3½	+	+	+	..	11	+	..	+	+	+	+	..	..	10	..	No eyebrows; improved on antisyphilitic therapy
4	Feit, H.: Med. Klin. **16**: 421, 1920	53	Gradual	Indefinite	+	..	+	..	..	..	..	+	+	..	..	+	..	..	..	Improved on antisyphilitic therapy
5	Büchler, P.: Ztschr. f. d. ges. Neurol. u. Psychiat. **72**: 207, 1921	29	Gradual with loss of weight	7	+	..	..	+22	..	..	..	+	+	..	+	..	+	8	..	No eyebrows; improved on syphilitic and pituitary extract; menses returned
6	Reye: Deutsche med. Wchnschr. **54**: 696, 1928; footnote 36	45	After puerperal sepsis	17	+	+	..	28	6	..	..	+	+	..	+	..	..	..	..	Basal metabolic rate, —49%
7	Zondek [43]	42	With amenorrhea	8	+	+	+	+34	..	..	..	+	+	+	+	+	..	..	..	Basal metabolic rate, 69 cc. of oxygen per minute
8	Plaut [44]	54	Gradual	15	+	+	..	..	..	+	..	+	+	..	..	+	+	..	..	Basal metabolic rate, —8%
9	von Gerlóczy [68]	18	After roentgen treatment of pituitary	1	+	+	..	..	..	..	..	..	..	..	..	..	..	..	+	
10	Szondy: Klin. Wchnschr. **2**: 902, 1923	49	No details	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
11	Reye [36]	34	After delivery with hemorrhage	6	+	+	..	+27	6	+	+	+	+	..	+	..	..	12	..	No eyebrows; basal metabolic rate, —34%; improved with pituitary therapy
12	Reye [36]	36	After birth of twins	3	+	+	..	+33	..	+	+	+	..	..	..	..	..	..	..	No eyebrows; cured by antisyphilitic therapy
13	Bauer [6]	22	Gradual	Indefinite	Mod. +	..	..	..	..	..	..	+	..	..	..	..	..	..	..	Spontaneous development of Simmonds' disease in pituitary dwarf
14	Suchier, W.: München. med. Wchnschr. **74**: 1795, 1927	21	After manual removal of placenta	..	Moderate	..	..	+	..	..	+	+	+	..	..	..	..	..	..	Improved on pituitary extract
15	di Guglielmo, G.: Bull. d. med.-chir. di. Pavia **2**: 167, 1927	29	After syphilis and diabetes insipidus	3	+	+	..	+26	..	..	..	+	+	+	+	..	..	+	..	Improved on pituitary extract
16	Herman, K.: Klin. Wchnschr. **7**: 944, 1928; Rev. franç. d'endocrinol. **6**: 301, 1928	53	Loss of weight	1	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Improved on pituitary extract
17	Rowe and Lawrence [18]	35	After complicated labor	3	+	..	..	+32	3	..	+	+	+	+	..	..	..	..	..	Improved on pituitary extract
18	Colden [3]	29	Signs of pituitary tumor	..	+	..	+	+20	..	..	..	..	+	+	..	..	..	..	+	
19	Riese [71]	40	Gradual with weakness	1	+	+	+	+	6	..	..	+	+	..	+	+	..	..	..	No eyelashes or eyebrows

* Although I believe that no case of Simmonds' disease can be accepted as definitely proved unless the clinical impression has been confirmed by a complete postmortem examination, yet I feel that the diagnosis can be made intra vitam with a high degree of accuracy. It is my plan to review briefly in this table the essential features of those cases that have been reported in the literature in which the diagnosis has not been submitted to autopsy confirmation, but in which the evidence seems convincing that the lesion lay in the anterior lobe of the hypophysis.

However, one should expect to find considerable emaciation. The greatest loss of weight recorded is in the case of Simons,[35] whose patient lost 51 Kg., or 63 per cent of her body weight. Losses of 40, 50 and 60 pounds (18.1, 22.7 and 27.2 Kg.) are not unusual. The distribution of the loss of weight is not constant and shows no characteristics valuable in the diagnosis.

Reye [36] has insisted that the clinical diagnosis can be made in the precachectic stage. He says that the patients have a slightly yellowish skin, resembling that seen in nephritis or pernicious anemia, and give one the impression of having a slight grade of myxedema. However, they are not helped by the administration of thyroid.

The patients present a fairly characteristic appearance. They are prematurely aged, the skin of the face is wrinkled, and this, combined with the loss of teeth and atrophy of the lower jaw, gives them a typical aged look. Another outstanding feature is the recession of the secondary skin characteristics. Women become amenorrheic, and there is usually a complete loss of libido. Complete amenorrhea at the age of 16 has been reported by Keilmann [37] and at 24 by Fahr [38] and Reiche.[39] The external genitalia, uterus and ovaries become atrophic. In men there is testicular atrophy with loss of libido and potency. The prostate and seminal vesicles undergo atrophic changes. The pubic and axillary hair becomes scant or falls out completely. The beard and moustache of men become sparse. Loss of eyebrows and eyelashes has been noted by many writers. There is usually a severe disturbance of dentition. It is interesting that the teeth are often lost without evidence of an advanced caries.

The patients are usually apathetic and easily exhausted. Dizziness, fainting and periods of unconsciousness are not uncommon. Convulsions are rare, but have been recorded. Mental disturbances are marked and may be the dominant clinical feature. The patients may be disoriented and require restraint. They have been observed on psychopathic pavilions as presenting cases of Korsakoff's syndrome.

Headache is a common complaint. There is no characteristic "pituitary headache" so far as the analysis of the cases allows. Vomiting is commonly associated with the headache even when no intracranial tumor is present.

Hypothermia is a quite constant finding, although there are case reports of a low grade fever. The temperature may range between

35. Simons: Zentralbl. f. d. ges. Neurol. u. Psychiat. **30**:125, 1922; **39**:191, 1925.
36. Reye: München. med. Wchnschr. **73**:902, 1926.
37. Keilmann: Centralbl. f. allg. Path. u. path. Anat. **32**:113, 1922.
38. Fahr, T.: Deutsche med. Wchnschr. **44**:206, 1918.
39. Reiche, F.: Med. Klin. **14**:984, 1918.

35 and 36 C. (95 and 96.8 F.) for months. Readings as low as 34 C. (93.2 F.) have been recorded by Grabe.[40]

The fundus oculi yields useful localizing information if there is an expanding intracranial lesion. As in other diseases of the pituitary region, the visual fields should be studied for color as well as for form.

The blood pressure is always low, and there is usually a bradycardia. Anemia is a constant finding, and the hemoglobin averages 50 per cent. The color index is usually less than 1. The leukocytes are often reduced in number. An eosinophilia,[41] which may reach 22 per cent, is an interesting and common finding. Hypoglycemia, as well as hyperchloremia, has been noted.

Roentgenograms should always be taken of the sella turcica. Evidences of a destructive, expanding lesion may be found, or one may find an unusually small sella. Lichtwitz [2] pointed out that cases of Simmonds' disease showed calcification in the pituitary region on roentgenograms. However, he had no postmortem controls, and later Reiche [42] was able to show that these shadows were not in the pituitary body but merely on the dura.

It is difficult to demonstrate the microsplanchnia during life, but the percussion outlines of the liver, heart and spleen, as well as the size of the heart, should be determined by roentgenograms.

Following the observation of Zondek,[43] the determination of the basal metabolic rate in Simmonds' disease has become important. It is always depressed. Records of minus 49 per cent have been obtained by Reye,[36] findings which are lower than those in complete myxedema. The specific dynamic action of a protein test meal should be determined. According to Plaut [44] and Kestner, Liebeschütz-Plaut and Schadow,[45] the increase in the oxygen consumption that usually follows a protein meal is either absent or much diminished in pituitary cachexia.

As Zondek [46a] pointed out, the ability of these patients to excrete water and salt is often embarrassed. One liter of water or 10 Gm. of sodium chloride is given and the excretion studied. Normally, the water should be excreted in four hours and the salt in twenty-four. In Simmonds' disease, there is usually a marked retention of both water and salt.

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40. Grabe: Deutsche med. Wchnschr. **49**:735, 1923.

41. Reiche.[39] Fahr.[38]

42. Reiche, F.: Med. Klin. **23**:1569, 1927.

43. Zondek, H.: Klin. Wchnschr. **1**:1385, 1922.

44. Plaut, A.: Deutsches Arch. f. klin. Med. **139**:285, 1922.

45. Kestner, O.; Liebeschütz-Plaut, R., and Schadow, H.: Klin. Wchnschr. **5**:1646, 1926.

46. (*a*) Zondek and Marx: Deutsche med. Wchnschr. **53**:598, 1927. (*b*) Jungmann, P.: Klin. Wchnschr. **2**:18, 1923.

Achylia gastrica has been noted several times,[39] and was present in the case here reported.

Differential Diagnosis.—The diagnosis of pituitary cachexia depends, to a large extent, on the absence of any of the other, more common causes of extreme loss of weight. If one can discover another adequate explanation for the cachexia, the diagnosis of Simmonds' disease should be made only with extreme reserve. However, in the cachexias secondary to tuberculosis, carcinoma or other conditions one does not find the recession of the secondary sex characteristics that is so marked in Simmonds' disease. Cachexia with the loss of pubic and axillary hair, especially if combined with atrophic genitalia and gonads and loss of sexual power, should attract attention to the pituitary gland as a possible source of the syndrome. It is noted that the loss of hair in the axillae and on the pubis is uncommon in the usual cachexias. If the history indicates that the illness began after childbirth, especially if the labor was difficult and accompanied by hemorrhage or followed by sepsis, one should be on the alert for a case of hypophyseal cachexia.

All authors note that the disease must be differentiated from the pluriglandular insufficiency of Claude and Gougerot[47] or the pluriglandular sclerosis of Falta.[10] At times this distinction may be impossible clinically, but the conditions can usually be separated. If one accepts pluriglandular sclerosis as a "simultaneous post inflammatory sclerosis of all the endocrine glands," one should expect symptoms referable to more than one gland. True cases of pluriglandular sclerosis, of which there are not many, show the skin and facies of myxedema as evidence of thyroid insufficiency. They may show the pigmentation of the skin and mucous membranes as well as the hypotension, hypoglycemia and adynamia that go with suprarenal failure. Tetany, latent or active, may reveal a parathyroid lesion, or glycosuria a sclerosis of the pancreas. Then, too, an etiologic factor for the disease may be found in syphilis or tuberculosis.

It is true clinically, and has been demonstrated pathologically many times, that destruction of the pituitary gives rise to secondary changes in the other glands. These alterations are most marked in the gonads, thyroid and suprarenals. However, these changes always follow the pituitary damage and are secondary to it, rather than simultaneous with it as is necessary in true pluriglandular sclerosis. Simmonds has shown that there can be extensive primary pituitary change with the other endocrine glands remaining normal.

Clinically, there are cases in which the pluriglandular involvement is so manifest that one cannot tell whether the glands were affected simultaneously or whether the changes in one produced the lesions in

47. Gougerot and Guy: Nouv. Icono. de l' Salpetière **24**:449, 1911. Claude and Gougerot: Compt. rend. Soc. de biol. **63**:785, 1907.

the other. In these cases only a careful, complete postmortem examination by a competent pathologist can determine the time relationship of the various lesions. However, although in some cases the clinical distinction between pluriglandular sclerosis and Simmonds' disease must await the pathologist's confirmation, in the majority of cases one can make the differential diagnosis clinically with a high degree of accuracy.

In separating cachexias of pituitary origin from others, the determination of the basal metabolic rate is often of great value. Depression of metabolism to levels lower than ever noted before has been reported in Simmonds' disease. This finding is of particular significance because in almost all other cachexias, especially those due to carcinoma and tuberculosis, the basal metabolic rate is usually elevated above the normal.

In short, one should suspect hypophyseal cachexia in every case of marked loss of weight. If careful clinical, roentgen and laboratory examinations reveal no other cause for the emaciation, one should be careful lest a case of Simmonds' disease be missed. The onset of symptoms after a complicated labor, loss of sexual function, falling out of axillary and pubic hair, loss of teeth, especially without caries, anemia with eosinophilia, hypotension, bradycardia, hypothermia, achylia gastrica, depression of the basal metabolic rate and loss of specific dynamic action of proteins are to be looked for. Of course, all these symptoms will not be found in any one case, but the presence of several of them is always suggestive.

If the observations of Reye,[48] Lichtwitz [2] and others are true, the improvement on treatment with anterior pituitary extract should be a valuable aid in the diagnosis.

PATHOLOGIC ANATOMY

If one accepts the premise that the anterior lobe of the pituitary gland has an irreplaceable function, then it is to be expected that destruction of this lobe will give rise to changes in the organism. I believe that the evidence is strong enough to accept the correlation of Simmonds' syndrome with a lesion destroying the anterior hypophysis. It follows that the symptoms should be fundamentally the same no matter what the nature of the process that results in the pituitary change. It has been shown that the recorded facts bear out these assumptions.

Simmonds [49] believed that most of the cases were due to infarction of the anterior lobe secondary to emboli. It was thought that embolic lesions of the pituitary were rare, but Simmonds was able to show that they were not uncommon and that the anterior lobe was more commonly

48. Reye: Deutsche Ztschr. f. Nervenh. **68**:153, 1921; footnote 36.
49. Simmonds, M.: Virchows Arch. f. path. Anat. **217**:226, 1914.

affected than the posterior in the ratio of seven to four. He also demonstrated that embolism to the anterior lobe results in anemic infarction because the vessels are functionally end-arteries. Merkel [50] demonstrated the pituitary gland in a case of sepsis in which seven eighths of the anterior lobe was destroyed, while the posterior lobe remained intact. Baló,[51] who studied postpartum embolism of the pituitary gland, came to the conclusion that small emboli usually had no functional significance, that ones of medium size gave rise to the clinical picture of Simmonds' disease, but that, following large embolic lesions, the death of the patient resulted before the development of any changes recognizable clinically.

The observation of Schlagenhafer [52] that tuberculosis of the pituitary with destruction can give rise to Simmonds' disease was made in 1916. In 1918, Froboese [53] noted tuberculous (?) destruction of part of the pituitary gland.

The clinical observation of Cyran,[54] later confirmed pathologically by Reinhardt [55] and Shereshevsky,[56] showed that symptoms of pituitary insufficiency may follow fractures of the skull with hemorrhage about the midbrain.

In 1919, Schaefer [57] reported a case of pituitary destruction due either to syphilis or to tuberculosis in which the syndrome of Simmonds developed. Jaffe [58] and Buday [59] were able to add cases due to gummas of the hypophysis.

Tumors, primary and secondary, of the hypophysis with Simmonds' syndrome have been reported by Simmonds,[33a] Lang,[60] Hönlinger and Stricker,[61] Pennetti,[62] Mogilnitzky [63] and Frazier.[29]

Postinflammatory destruction of undetermined origin has been reported by von Monakow [64] and Pribram.[27]

50. Merkel, H.: Verhandl. d. deutsch. path. Gesellsch. **17**:193, 1914.
51. Baló, J.: Beitr. z. path. Anat. u. z. allg. Path. **72**:599, 1923-1924.
52. Schlagenhafer: Virchows Arch. f. path. Anat. **222**:249, 1916.
53. Froboese, C.: Centralbl. f. allg. Path. u. path. Anat. **29**:145, 1918.
54. Cyran: Deutsche med. Wchnschr. **45**:1261, 1918.
55. Reinhardt: Klin. Wchnschr. **1**:2309, 1922.
56. Shereshevsky, N. A.: Vrach. delo, Kkarhov **8**:1093, 1925; Centralbl. f. d. ges. Neurol. **42**:434, 1925.
57. Schaefer: Dissertation, Path. Inst., Jena, 1919; Centralbl. f. allg. Path. u. path. Anat. **30**:520, 1920.
58. Jaffe: Frankfurt. Ztschr. f. Path. **27**:324, 1922.
59. Buday: Klin. Wchnschr. **2**:902, 1923.
60. Lang, F. J.: Wien. klin. Wchnschr. **37**:977, 1924.
61. Hönlinger, H., and Stricker, W.: Frankfurt. Ztschr. f. Path. **29**:492, 1923.
62. Pennetti, G.: Riforma med. **44**:9, 1928.
63. Mogilnitzky, B. N.: Virchows Arch. f. path. Anat. **269**:1, 1928.
64. von Monakow, P.: Verhandl. d. deutsch. Kong. f. inn. Med. **34**:361, 1922.

Keilmann [37] reported a case due to destruction of the hypophysis by a large cyst weighing 93 Gm. Kiyono [65] also noted a case due to a hypophyseal cyst.

There is some evidence to believe that the case reported by Hochstetter and Veit [66] had as its pathologic basis a lipoid granuloma of the type found in the Hand-Schüller-Christian syndrome.[67]

Von Gerlóczy [68] reported the appearance of cachexia and anemia in a pituitary dwarf who had been subjected to intensive irradiation of the hypophyseal region. However, Gordon Holmes [69] and Julius Bauer [6] noted the spontaneous appearance of Simmonds' disease in pituitary dwarfs.

Destruction of the pituitary gland by a metastatic abscess has been noted in a case of hypophyseal cachexia by Jungmann.[46b] Hirsch and Berberich [70] reported a case due to destruction of the gland by hemorrhage.

Reye [36] expressed the belief that pituitary atrophy is secondary more commonly to thrombosis than to embolism, especially in cases without definite sepsis.

Maresch [34] called attention to the fact that the appearance of hypophyseal cachexia is common after repeated labors, particularly if they follow in close succession, and suggested a functional exhaustion of the pituitary gland as a cause for the syndrome.

In Riese's case [71] the mother of the patient had had symptoms suggestive of pituitary disease, and the author suggests that there may be a constitutional weakness of the pituitary gland which becomes obvious if it is subjected to great strain as in repeated pregnancies.

So much for the pathologic changes found in the hypophysis itself in Simmonds' disease. There is usually associated a secondary atrophy of the thyroid, gonads and suprarenal cortex. This may, however, be absent. Attention has already been called to the unusual smallness of the viscera or microsplanchnia first noted by Simmonds. Meng [72] was able to demonstrate marked atrophy of the hair follicles and sweat glands in his case of pituitary cachexia. Altmann [73] called attention to the common association of some degree of pulmonary tuberculosis with Simmonds' disease.

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65. Kiyono, H.: Virchows Arch. f. path. Anat. **252**:118, 1924.

66. Hochstetter, F.: Med. Klin. **18**:647, 1922. Veit, B.: Frankfurt. Ztschr. f. Path. **28**:1, 1922.

67. Chester, W.: Virchows Arch. f. path. Anat. **279**:561, 1930.

68. von Gerlóczy, G.: Klin. Wchnschr. **2**:902, 1923.

69. Holmes, Gordon: Brit. M. J. **2**:1037, 1926.

70. Hirsch, S., and Berberich, J.: Klin. Wchnschr. **3**:483, 1924.

71. Riese, H.: Med. Welt **3**:1546, 1929.

72. Meng, H.: Frankfurt. Ztschr. f. Path. **36**:650, 1928.

73. Altmann, F.: Frankfurt. Ztschr. f. Path. **36**:393, 1928.

When a distinct clinical syndrome accompanies the destruction of the anterior lobe of the hypophysis, it assumes the form described by Simmonds. However, there can be extensive, almost complete destruction of the pituitary gland, and no characteristic symptoms may be noted. Such destruction of the hypophysis without clinical symptoms has been noted by Markel,[50] Krumbhaar,[74] Worms and Delater,[26] Kiyono[75] and Broussilovski.[76]

Although it is quite obvious that the syndrome of Simmonds' disease depends on the absence of the anterior lobe of the hypophysis, no one has attempted to correlate the disease with any one of the three specific cells found in the pituitary.

It is now established that acromegaly depends on the hyperactivity of the eosinophilic elements, and it is perhaps not unlikely that Simmonds' disease has as its physiologic basis a *hypofunction* of these same cells. At least, one might expect something of this nature from the directly opposite clinical pictures presented by acromegaly and Simmonds' disease.

It is unlikely that the basophilic cells have any relation to the syndrome. The presence of a large number of these cells in an adenoma (Simmonds) was unable to protect against the development of the clinical picture.

Another clinical observation implicating the eosinophilic cells is to be found in the course of some cases of acromegaly. These start as typical acromegalias and then later asthenia, cachexia, loss of gonadal function and loss of pubic and axillary hair develop and the patients finally die in extreme cachexia. In these patients it seems logical to postulate an exhaustion of the previously hyperactive eosinophilic tissue as the cause for the appearance of the features suggesting Simmonds' syndrome.

In the future it would be advisable to utilize every opportunity to study the relative proportion of the various cells in all cases of Simmonds' disease to see whether an eosinophilic deficiency is the basis of the syndrome.

PATHOLOGIC PHYSIOLOGY

The entire knowledge regarding the relation of the pituitary gland to clinical medicine is quite recent. Although Marie[77] first recognized acromegaly as a clinical picture, it was Minkowski[78] who first associated this syndrome with a lesion of the pituitary body. In 1894,

74. Krumbhaar, E. B.: M. Clin. North America **5**:927, 1921.

75. Kiyono, H.: Virchows Arch. f. path. Anat. **259**:388, 1926.

76. Broussilovski, L.: Encéphale **20**:734, 1925.

77. Marie: Rev. de méd. **6**:297, 1886.

78. Minkowski: Berl. med. Wchnschr. **21**:371, 1887.

Tamburini [79] recorded the common association of changes in the eosinophilic cells of the anterior lobe with acromegaly. Since this time acromegaly has been considered as a hyperfunction of the anterior lobe, or at least part of it. Recently, Putnam, Benedict and Teel [80] have been able to produce acromegaloid features in dogs by the injection of extracts from the anterior lobe.

Until Simmonds no one believed that there was a clinical picture associated with a lowered or absent function of the anterior lobe. I believe it has been shown that Simmonds' contention was correct and that one should consider the relationship between acromegaly and Simmonds' disease in the same light that myxedema and hyperthyroidism or tetany parathyreopriva and osteitis fibrosa of Recklinghausen are viewed. It is necessary to recall only that acromegaly is characterized by overgrowth, splanchnomegaly and increase in the size of the pituitary gland, whereas pituitary cachexia is marked by cachexia, microsplanchnia and destruction of the gland.

The classic experiments of Cushing [81] and his school showed that after hypophysectomy in dogs there intervened a state of "cachexia hypophyseopriva," characterized by failure to grow, loss of weight and gonadal atrophy. Although it is true that Camus and Roussy [82] and Bailey and Bremer [83] have adduced evidence to show that many of the findings attributed by Cushing to the removal of the pituitary may have been a result of injury to the hypothalamic region, yet it is a fact that hypothalamic damage does not explain all Cushing's findings. The recent work of Smith [84] in which, by a new technic, he was able to excise the pituitary in rats without the possibility of injury to the midbrain shows that cachexia and genital atrophy are direct consequences of removal of the pituitary gland. Smith [85] could also produce in his rats a distinct premature senility that recalls the picture seen clinically in Simmonds' disease.

Goetsch [12] has noted that in the operative removal of the anterior lobe of the pituitary there is a permanent decrease in the number of Leydig's cells and a lack of spermatogenesis. This information, coupled

79. Tamburini: Riv. sper. di freniat. **20**:559, 1894.

80. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Extract, Arch. Surg. **18**:1708 (April) 1929.

81. Cushing, H.: Bull. Johns Hopkins Hosp. **21**:127, 1910.

82. Camus, J., and Roussy, G.: Endocrinology **4**:507, 1920.

83. Bailey, Percival, and Bremer, Frédéric: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

84. Smith: Anat. Rec. **32**:221, 1926.

85. Smith, P. E.: Disabilities Caused by Hypophysectomy and Their Repair, J. A. M. A. **88**:158 (Jan. 15) 1927.

with the recent work of Zondek and Ascheim, leaves no doubt that the anterior lobe is the "motor" of the gonads and that normal sexual function depends on an intact pituitary gland. It is now quite clear why cases of Simmonds' disease show symptoms of lowered sexual activity. Early loss of menses, sterility, loss of libido and gonadal atrophy as they occur in this disease are probably the result of the absence of the stimulus that is normally supplied by the anterior pituitary lobe.

The relationship of the anterior lobe of the pituitary gland to the basal metabolic rate cannot be said to have been completely studied. However, there is good clinical evidence to show that lesions in this region give rise to a depression of the basal metabolic rate.[86] In fact, readings lower than those found in complete myxedema have been reported.

Plaut [44] studied three cases of pituitary cachexia and found the metabolism depressed in all. As a result of her extensive investigation she gives the following tabulation:

Disease	Basal Metabolic Rate	Specific Dynamic Value
Starvation	Normal or low	Low
Hypophyseal obesity	Normal	Low
Hypophyseal cachexia	Low	Low
Myxedema	Low	Normal
Exophthalmic goiter	High	Variable
Usual cachexias	High	Unknown
Constitutional underweight	Normal	Increased

Plaut points out that the basal metabolic rate may be a useful aid in differentiating the cachexia of pituitary origin from that due to carcinoma, tuberculosis and other conditions. In these states the basal rate is always elevated, but in Simmonds' disease it is always reduced, often to extreme levels. Høboll [87] reported that sixteen of nineteen patients with carcinomas of the gastro-intestinal tract had an elevation of the basal metabolic rate. The highest level recorded was plus 51.3 per cent. Strieck and Mulholland [88] noted a basal metabolic rate of plus 58 per cent in a case of metastasizing carcinoma of the stomach.

It should be noted, however, that some observers have noted a low basal metabolic rate in cachexia not of pituitary origin. Joslin [89] reported the cases of emaciated diabetic patients with basal rates of minus 40 per cent.

86. Buentin: J. Physiol. **71**:xxvii, 1931. Reye.[36] Zondek.[43]

87. Høiboll, S. A.: Acta med. Scandinav. **72**:475, 1929.

88. Strieck, F., and Mulholland, H. B.: Deutsches Arch. f. klin. Med. **162**:51, 1928.

89. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 3, Philadelphia, Lea & Febiger, 1923.

In regard to changes in the specific dynamic value of the foodstuffs, the findings are not so constant. Kestner, Liebeschütz-Plaut and Schadow [45] expressed the belief that there is always a depression in Simmonds' disease. Other observers [6] have not been able to confirm these findings. In hypophysectomized rats, Smith [90] found the specific dynamic action of the proteins to be absent. Evidence to support the rôle of the pituitary in the determination of the basal metabolic rate is to be had from the cases of Simmonds' disease in which the patients were treated with active extracts from the anterior lobe. An increase in the consumption of oxygen from 69 cc. per minute to 149.2 cc. per minute has been recorded.[91] It is interesting that Knipping [92] found that the specific dynamic action of the protein was always decreased during pregnancy. He suggests that this may be associated with the pituitary changes that occur at this time and may possibly be due to a redistribution of the pituitary cells.

Zondek and Marx [46a] were able to demonstrate distinct disturbances in the ability of patients with pituitary cachexia to excrete water and salt normally.

Changes in the growth of body hair have been noted in Simmonds' disease since the original description. In this connection it is interesting to note that Benedict, Putnam and Teel [93] were able to show that there were disturbances in the growth of the hair of dogs after hypophysectomy.

Schellong [94] has recently pointed out that the attacks of collapse and unconsciousness so often observed in Simmonds' disease are the result of the sudden drop in blood pressure that follows exertion in these patients, even if the original blood pressure level is normal. Schellong believes that this paradoxical blood pressure reaction is a symptom of insufficiency of the anterior pituitary lobe and a valuable aid in diagnosis. This observation is interesting and should be confirmed.

THERAPY

As in most other conditions in which the clinical course is irregular, the evaluation of any one form of therapy offers difficulties. When one recalls that untreated patients may live as long as forty-four years [95]

90. Foster, G. L., and Smith, P. E.: Hyophysectomy and Replacement Therapy, J. A. M. A. **87**:2151 (Dec. 25) 1926.

91. Zondek, H.: Die Krankheiten der Endokrinen Drüsen, Berlin, Julius Springer, 1923.

92. Knipping, H. W.: Arch. f. Gynäk. **116**:520, 1923.

93. Benedict, E. B.; Putnam, T. J., and Teel, H. M.: Am. J. M. Sc. **179**:489, 1930.

94. Schellong, F.: Klin. Wchnschr. **10**:100, 1930.

95. Reiche, F.: Med. Klin. **26**:1447, 1930.

after the onset of symptoms, one must regard with caution statements regarding benefits derived from any special form of therapy.

In his original descriptions Simmonds pointed out that replacement therapy with the anterior lobe of the pituitary was indicated and should be tried. This, in the form of prephyson, has yielded excellent results in the hands of Reye, Zondek and Lichtwitz. However, the results do not seem conclusive enough to enable one to speak of a "specific" for this disease in the manner that one regards thyroid extract in the treatment of myxedema.

If syphilis is present, it should be treated vigorously, as recession of the clinical picture under antisyphilitic therapy has been observed.

An expanding intracranial tumor compressing the anterior pituitary lobe may often be approached surgically, and temporary alleviation, at least, is offered.

To combat the extreme cachexia and anorexia that is present in this disease, general hygienic and dietetic measures should be followed. In addition, the careful administration of insulin (Falta) in doses of from 2 to 20 units subcutaneously one-half hour before meals may be a useful aid in increasing the weights of the patients.

As the disease often appears post partum, usually in cases with obstetric complications, it would seem logical to advise careful management of the delivery and puerperium by a competent obstetrician to avoid this complication.

SUMMARY

Attention has been called to a syndrome not frequently encountered in the English literature and one that I believe to be more common than is generally accepted. In its fully developed form it is readily recognized by the association of extreme cachexia with signs and symptoms of gonadal atrophy. The onset is often consequent on a complicated labor, and among the clinical features may be mentioned premature aging, early and complete amenorrhea, loss of pubic and axillary hair, atrophy of the lower jaw with loss of teeth and a profound depression of the basal metabolic rate.

In addition to the advanced obvious cases, attention should be directed to mild, abortive forms that masquerade under such diagnoses as arteriosclerotic cachexia, syphilitic cachexia and latent tuberculosis.

The physiologic significance of disease in the pituitary region is great, and much can be learned from observing closely patients presenting signs of pituitary cachexia.

Dr. B. S. Oppenheimer, physician to Mount Sinai Hospital, from whose service the case reported came, has made this publication possible. Dr. J. H. Globus, neuropathologist to the hospital, allowed me to use the sections and gave many helpful suggestions. Dr. R. T. Frank supplied figure 4.

124 East Sixty-First Street.

EXPERIMENTAL EDEMA IN NEPHRECTOMIZED DOGS

II. THE RÔLE OF WATER AND CHLORIDES

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AND

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Lyon, Shafton and Ivy [1] found that it was possible to produce edema in bilaterally nephrectomized dogs and at the same time to prolong the life of such animals by the subcutaneous administration of Ringer's solution. It was observed that on the second or third day vomiting and diarrhea resulted, which led to dehydration and hypochloremia. The Ringer's solution relieved this condition and presented water and chlorides for the formation of edematous fluid.

The following questions naturally arose from this work: Which was most important in the production of the edema, water or chlorides? Was the edema, possibly by acting to dilute "toxins," responsible for the prolongation of life, or was the prolongation of life due simply to the relief of the dehydration and hypochloremia? We desired to answer these questions and believed that the water factor could be controlled by the use of a solution of dextrose instead of Ringer's solution, and that the chloride factor could be controlled by adding various amounts of Ringer's solution to the solution of dextrose. Our results show that the water alone is not responsible for the edema, and that edema is not necessary for the prolongation of life.

METHODS

In these experiments healthy dogs varying in weight from 35 to 50 pounds (from 1,600 to 2,300 Gm.) were subjected to bilateral nephrectomy. The operations were performed under strict asepsis, with ether anesthesia; the kidneys were removed through an abdominal incision. The solutions injected were Ringer's solution (consisting of sodium chloride, 0.9 per cent; potassium chloride, 0.042 per cent; calcium chloride, 0.024 per cent, and sodium bicarbonate, 0.02 per cent) and a 4 per cent solution of dextrose specially prepared for intravenous injections. The solutions and apparatus were sterilized before use. The regular laboratory diet was offered to the dogs each day. Blood drawn for analysis and venesection was

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1. Lyon, E. E.; Shafton, A. L., and Ivy, A. C.: Arch. Int. Med. **44**:424 (Sept.) 1929.

taken from the saphenous vein by needle and syringe. Hypodermoclysis was performed in the scapular region.

The volume of solution injected varied from 1,500 to 2,000 cc., i. e., about 90 cc. per kilogram. This volume was arrived at by observing the daily water intake of large dogs and by approximating the amount of water lost in the vomitus, stools and respiration. That it was not excessive is seen from the experimental results given in the following paragraphs.

EXPERIMENTS AND RESULTS

Seven groups of experiments were performed in this study.

TABLE 1.—*Results of Administration of Ringer's Solution Subcutaneously to Nephrectomized Dogs*

No.	Lived, Hours	Anasarca, Day	Ascites, Cc.	Hydrothorax, Cc.	Hydropericardium, Cc.	Diarrhea, Day	Vomiting, Day	Salivation, Day
1*	158	4th	..	..	..	4th	4th	None, no autopsy
2	110	3d	50	20	20	4th	3d	None
3	123	4th	40	10	25	5th	2d	5th
4	167	5th	1,200	None	15	3d	2d	None
5	130	4th	175	40	4	4th	5th	None
6	231	3d	1,800	75	15	4th	2d	7th
7	221	6th	50	20	10	5th	3d	None
8	158	4th	100	20	3	3d	4th	None
9	108	4th	None	None	None	3d	3d	3d
Average	156.2							

* Dog removed before autopsy was made.

TABLE 2.—*Showing that Water Alone Does not Produce Edema in Bilaterally Nephrectomized Dogs* *

No.	Lived	Anasarca	Salivation	Diarrhea, Day	Vomiting Day	Change in Weight, Pounds
1	92 hrs., 40 min.	None	None	None	2d	Lost 2 (900 Gm.)
2	104 hrs., 45 min.	None	None	None	2d	Lost 1.5 (700 Gm.)
3	137 hrs.	None	None	4th	4th	
4	94 hrs., 30 min.	None	None	2d	None	
5	87 hrs., 48 min.	None	3d day, slight	2d	None	
Average	103 hrs.					

* Group 3; these dogs received from 1,500 to 2,000 cc. of a 4 per cent solution of dextrose daily by hypodermocylsis.

GROUP 1.—The dogs in this group were given no postoperative treatment and served as controls. There were five dogs in the group, the length of life being from 65 to 154 hours. The average length of life was 108.8 hours, which compares favorably with the average of 105 hours obtained by Lyon, Shafton and Ivy.

GROUP 2.—The dogs in this group were given from 1,500 to 2,000 cc. of Ringer's solution subcutaneously each day. There were nine dogs in the series, the length of life being from 108 to 231 hours, with an average of 156.2 hours. The results are recorded in table 1.

Edema developed in all the dogs; ascites and hydropericardium developed in all but two, and hydrothorax developed in all but three. The average length of life was prolonged.

Group 3.—The dogs in this group were given subcutaneous injections of from 1,500 to 2,000 cc. of a 4 per cent solution of dextrose daily. They lived from 88 to 137 hours. The average length of life was 103 hours. There were five dogs in the group. The results are recorded in table 2. Edema developed in none of the dogs of this group. The average length of life was not prolonged; this shows that dehydration is not the cause of early death in nephrectomized dogs, because these dogs were not dehydrated and died in the same length of time as untreated nephrectomized dogs.

Group 4.—These dogs (there were five dogs in the group) were given daily subcutaneous injections of from 1,500 to 2,000 cc. of a 2:1 mixture of Ringer's solution and a 4 per cent solution of dextrose. The results are recorded in table 3.

Table 3.—*Results with a Mixture of Two Thirds of Ringer's Solution and One Third of a 4 Per Cent Solution of Dextrose Subcutaneously Administered to Nephrectomized Dogs*

No.	Lived, Hours	Anasarca	Ascites, Cc.	Hydrothorax, Cc.	Hydropericardium, Cc.	Diarrhea, Day	Vomiting, Day	Salivation, Day	Blood Chlorides
1	120	None	None	None	2	Slight, 4th	None	None	0.481 0.556
2	127½	All legs, scrotum and chest	100 fluid	10, each side	3, clear fluid	5th	4th	None	0.478 0.498
3	223	General, 6th day	200	15, each side	25, clear fluid	6th	5th	9th	0.478 0.490
4	130	None	None	10, each side	None	None	None	None	
5	206	None	None	None	2	6th	6th	6th	0.469 0.525
Aver.	161								

Blood was drawn from the saphenous vein daily for analysis. The blood chlorides were found either to remain normal or to show a slight increase. In two dogs a general edema with ascites developed. The average length of life was prolonged.

Group 5.—There were nine dogs in the series. They were given daily injections of from 1,500 to 2,000 cc. of a 1:2 mixture of Ringer's solution and a 4 per cent solution of dextrose. The results are recorded in table 4.

The average length of life was 161 hours; that is, life was prolonged. Only one dog showed any sign of edema of the skin, and that was very slight, while three showed ascitic fluid; six hydropericardial fluid, and one, fluid in the pleural cavity. The blood chlorides, which were followed in five animals, were normal or somewhat reduced.

Group 6.—There were three dogs in the series, the length of life being from 91 to 239 hours. They were given daily injections of 1,500 cc. of equal amounts of a 4 per cent solution of dextrose and Ringer's solution. Edema (550 cc. of ascitic fluid) was seen in but one of the three, and only after the fifth day postoperatively. The chlorides were followed, and were observed to remain practically normal.

TABLE 4.—*Results on Administration of a Mixture of One Third Ringer's Solution and Two Thirds of a 4 Per Cent Solution of Dextrose*

No.	Lived, Hours	Anasarca	Ascites, Cc.	Hydrothorax, Cc.	Hydropericardium, Cc.	Diarrhea, Day	Vomiting, Day	Salivation, Day	Blood Chlorides
1	124	None	None	None	None	None	None	4th	
2	228	None	25	None	15	6th, until death	6th, until death	7th, until death	
3	100	None	None	None	15	3d, until death	2d, until death	2d, until death	
4	91	None	15	None	None	None	None	None	
5	93	None	None	None	5	None	None	None	0.467
6	90	Very slight, of scrotum	None	None	5	None	None	None	0.304
7	227	None	25	10	125	8th, until death	6th, until death	8th, until death	0.353
8	248	None	None	None	None	5th, until death	6th, until death	6th, until death	0.504
9	255	None	None	10	3	5th, until death	4th, until death	4th, until death	0.488
Aver.	161								

TABLE 5.—*Effect of Venesection Plus Ringer's Solution (Group 7)*

No.	Lived, Hours	Anasarca, Day	Ascites	Hydrothorax	Diarrhea, Day	Vomiting, Day	Salivation, Day	Weight, Pounds
1	147	6th	Present	Present	None	5th	6th	Gained 5.5 (2,500 Gm.)
2	108	None	None	None	4th	4th	None	
3	158	4th, fore legs	None	None	5th	5th	None	
4	250	4th, fore legs	Present	Present	4th	4th	8th	Gained 18 (8,200 Gm.)
Average	165.6							

TABLE 6.—*Summary of Results*

Group	No. of Dogs	Procedure	Length of Life, Hours	Edema
1	5	Control (bilateral nephrectomy).....	108.8	Not produced
2	9	Bilateral nephrectomy and Ringer's solution subcutaneously	156.2	Produced
3	5	Bilateral nephrectomy and a 4 per cent solution of dextrose subcutaneously	103	Not produced
4	5	Bilateral nephrectomy and a mixture of Ringer's solution and a 4 per cent solution of dextrose, 2:1, subcutaneously	161	Produced in 2 of 5
5	9	Bilateral nephrectomy and a mixture of a 4 per cent solution of dextrose and Ringer's solution, 2:1, subcutaneously	161	Produced in 1 of 9
6	3	Bilateral nephrectomy and a mixture of equal amounts of Ringer's solution and a 4 per cent solution of dextrose subcutaneously	158.6	Produced in 1 of 3
7	4	Bilateral nephrectomy and Ringer's solution subcutaneously, with venesection, daily	165.6	Produced in 3 of 4

GROUP 7.—There were four dogs used in the experiment. They were given daily 1,500 cc. of Ringer's solution subcutaneously, and venesection was done, the amount of blood being from 40 to 100 cc. daily. The dogs lived from 108 to 250 hours. Table 5 shows the results.

Edema developed in three of the four dogs, and two showed ascites and hydrothorax. Two dogs showed a gain in weight. Venesection was not of any appreciable benefit.

COMMENT ON RESULTS

In the first or control group of untreated, bilaterally nephrectomized dogs the average length of life was found to be 108.8 hours, which compares closely with the observation of Lyon, Shafton and Ivy, of 105.6 hours.

In the second group the average length of life was found to be 156.2 hours with the subcutaneous administration of the Ringer's solution, as compared with 165 hours for the animals in Lyon's series when the same procedure was followed.

In the third group, a 4 per cent solution of dextrose was administered subcutaneously in order to observe the effect of a volume of water equal to that given in Ringer's solution without the salt factor, the dextrose being oxidized. It was found that there was no production of edema, and that the length of life was practically that of the untreated dogs, or 103 hours.

In the fourth, fifth and sixth groups, mixtures of Ringer's solution and a 4 per cent solution of dextrose were given in an attempt to determine the amount of salt required to produce edema. The question is whether edema will develop if salts are replaced sufficiently to balance the amount lost by vomiting and diarrhea, or whether more than this amount is necessary. It was found that with the three mixtures of dextrose and Ringer's solution that were used, life was prolonged to the same extent as it was in the dogs receiving Ringer's solution only, but that there was a marked decrease in the edema produced, only four dogs showing any sign of edema. It is evident that if the chlorides, or salt factor, are controlled so that the blood chlorides remain about normal, edema does not result. In order to obtain edema, excess salt must be administered. Ringer's solution when administered alone provides the necessary excess salt.

In the seventh group, venesection was tried, with the injection of Ringer's solution in an attempt to remove some of the toxic products that might have accumulated. The amount of blood lost was amply replaced by Ringer's solution. The average length of life of the dogs in this group was 165.6 hours or slightly but not significantly longer than those treated with Ringer's solution alone in our experiments, and practically the same as those treated with Ringer's solution alone

in Lyon, Shafton and Ivy's work. It is possible that the quantity of blood removed was not large enough, but it amounted to from one twenty-fifth to one tenth of the total blood volume daily.

These experiments demonstrate the important rôle that sodium chloride plays and the rather minor rôle that water and the products of nitrogenous retention play in the production of edema. In the presence of marked nitrogenous retention, water in "balanced" amounts is not retained in the body if the blood chlorides are subnormal. By keeping the input of water constant and controlling the input of sodium chloride in nephrectomized dogs, one can control the presence or absence of edema. There is apparently no strict relation between the level of the blood chlorides and the occurrence of edema, since edema may or may not be present with a normal level of blood chlorides, but in the absence of edema the blood chlorides are low. There is, however, a definite relation between the input of sodium chloride and the occurrence of edema.

These results, in our opinion, prove the contention of Widal [2] that although the retention of urea and other nitrogenous substances is responsible for uremia, it is not significant in the development of edema. We shall report evidence in a later paper to show that nitrogenous retention increases capillary permeability. Obviously, in these experiments we are dealing only with extrarenal factors.

The cause of death in nephrectomized dogs is unquestionably the retention of the substances normally eliminated by the kidneys. The fact that the nephrectomized dogs treated with a solution of dextrose alone did not live longer than untreated controls appears to indicate that dehydration per se is not an important contributory cause of death, since the dogs were receiving plenty of water. A loss of weight occurred in these dogs, which showed that no invisible retention of water occurred, whereas in the dogs which received the mixture of Ringer's solution and dextrose solution and in which edema did not occur the loss of weight was not so marked. It therefore appears that the dogs given dextrose solution were somewhat dehydrated, or that they could not retain the water because of a deficiency in sodium chloride. This indicates that the hypochloremia was the prime factor; that is, in order to obtain a retention of water adequate to prevent dehydration, sufficient sodium chloride had to be given to prevent hypochloremia; if an excess was given, edema resulted. We therefore conclude that the prolongation of life is due primarily to maintenance of the normal balance of water, sodium and chlorides in the body, and not primarily to a dilution of the urinary or toxic substances retained. The slower rate

2. Widal, F., and Lemierre, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **20**:785, 1903.

of accumulation of nitrogenous products, as shown by the analysis of the blood of dogs treated with Ringer's solution in the work of Lyon, Shafton and Ivy, is most probably due to the absence of dehydration, which is known to increase the nitrogenous content of the blood, because it is probable that dehydration per se promotes proteoclastic changes in the cells.

Our results indicate not only that the intake of sodium chloride should be limited in nephritis, a well known fact, but also that if a patient with nephritis has vomited so much that hypochloremia exists, which is probably rare, the patient should be benefited by the proper or controlled administration of dextrose and sodium chloride.

CONCLUSIONS

1. Ringer's solution (from 1,500 to 2,000 cc. for dogs weighing from 35 to 50 pounds [from 1,600 to 2,300 Gm.]) injected subcutaneously in bilaterally nephrectomized dogs produces edema and prolongs life for an average of sixty hours.

2. A similar volume of a 4 per cent solution of dextrose injected subcutaneously into bilaterally nephrectomized dogs neither prolongs life nor produces edema.

3. The same volume of mixtures of Ringer's solution and a 4 per cent solution of dextrose, containing sufficient salt to maintain the blood chlorides at a normal level, does not produce edema consistently when injected subcutaneously into bilaterally nephrectomized dogs. It does, however, prolong life.

4. Venesection (from $\frac{1}{25}$ to $\frac{1}{10}$ of total volume of blood daily) did not prolong the life of nephrectomized dogs receiving Ringer's solution.

5. Our results show that the prolongation of life is due primarily to maintenance of the normal water-sodium-chloride balance in the body, and not to a dilution by edematous fluid of the urinary or toxic substances retained.

6. Edema does not occur in bilaterally nephrectomized dogs until water with excessive sodium chloride is supplied.

7. The retention of urinary products per se in the presence of hypochloremia (chiefly sodium chloride) is not conducive to edema, even when adequate water is supplied; this confirms the contention of Widal.

INFLUENCE OF THE PITUITARY GLAND ON ERYTHROCYTE FORMATION

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DETROIT

In this article we shall endeavor to show that: (*a*) The pituitary secretion has a very important influence on erythrocyte formation. (*b*) *Primary* disease of the suprarenal cortex results in *secondary* pituitary changes, thus accounting for many signs and symptoms erroneously ascribed to the suprarenal cortex. (*c*) The specific and selective embryohormonic relations of the pituitary gland to mesodermal tissues is a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances.

Two cases of polycythemia vera with pituitary basophilism, coming to autopsy, and polycythemias experimentally induced in dogs by bilateral adrenalectomy form the basis of our report.

Our interest in the erythropoietic function of the pituitary was the result of some clinical observations which pointed to this gland as the major factor in stimulating the hematopoietic system to erythrocyte formation.

While we were engaged in carrying out the experimental part of the work, a splendid article by Cushing [1] appeared, in which he reported twelve cases of pituitary basophil adenomas, associated with, among other things, a tendency to polycythemia. Two were his own, the remaining ten being reported by others (Turney, Anderson, Riechmann, Zondek, Parkes-Weber, Teel, Friedman, Mooser, Raab-Krause and Wieth-Pedersen). Death occurred in nine cases, eight of which came to autopsy. A basophilic adenoma of the pituitary was found in three cases, an undifferentiated adenoma in two cases and an adenomatous-like structure in a fibrosed area of the anterior pituitary in one case; two patients were said to be "normal."

1. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**: 137, 1932.

Cushing gave the following features as characteristic of all cases:

(1) A rapidly acquired, peculiarly disposed and usually painful *adiposity* (in one instance representing a 40 per cent gain in weight), confined to the face, neck and trunk, the extremities being spared; (2) a tendency to become *round-shouldered* (kyphotic) even to the point of measurable loss of height associated with lumbo-spinal pains; (3) a sexual dystrophy, shown by early *amenorrhea* in the females and ultimate *impotence* in the males; (4) an alteration in normal hirsuties, shown by a tendency to *hypertrichosis* of the face and trunk in all the females as well as in preadolescent males and possibly the reverse in adult males; (5) a dusky or plethoric appearance of the skin with *purplish lineae atrophicae;* (6) *vascular hypertension;* (7) a tendency to *erythremia;* (8) variable *backaches, abdominal pains, fatigability* and ultimate extreme *weakness.*

That certain cerebral conditions may lead to polycythemia is becoming recognized with greater frequency. Günther [2] stated that certain clinical observations lead to the question whether or not there is a cerebral regulating center for the blood-forming organs. He said that it is within the range of possibilities that the working mechanism of this center stands in relationship to the endocrine system, so that a physiologic separation is hardly possible. He reports a case of cerebral polycythemia in a 26 year old man with marked obesity, hypotrichosis, hyposexuality, headaches, vasomotor upsets, respiratory disturbance, narcolepsy and psychic disturbances. The spleen was not enlarged, and there was no hypertension.

Etiologically Günther considered that the condition is due to a basal disturbance between the third ventricle and the hematopoietic system, the exact nature of which is still in doubt. Furthermore, he said that there is a close relationship between the endocrine system, particularly the suprarenals, so that at present it is impossible to decide whether the condition is a primary cerebral or an endocrine disturbance.

Guillain, Lechelle and Garcin [3] reported five cases of polycythemia which seemed to originate in the region of the pituitary and tuber cinereum. This report was based on clinical symptoms usually associated with disturbances in and around the pituitary.

Nathan [4] recently called attention to the diencephalic area as possibly being responsible for polycythemia.

Castex [5] believes that Geisböck's disease (polycythemia with hypertension) is probably a diencephalic syndrome.

2. Günther, Hans: Ueber zerebrale Polyglobulie, Deutsches Arch. f. klin. Med. **16**:41, 1930.

3. Guillain, G.; Lechelle, P., and Garcin, R.: La polyglobulie de certains syndromes hypophysaires et hypophyso-tubériens, Compt. rend. Soc. de biol. **106**: 515, 1931.

4. Nathan, M.: Erythrémies protopathiques et diencéphale, Presse méd. **39**: 403, 1931.

5. Castex, M. R.: La hypertension arterial, Buenos Aires, Humberto Andrecetta, 1929.

Schulhof's and Matthies'[6] work on polycythemia of cerebral origin was stimulated by Schulhof's observations in 1920, when he noticed polycythemia in cases of epidemic encephalitis. These authors found that polycythemia of long duration, induced by a lesion of the proximal part of the vegetative centers of the brain in rabbits, indicates that the brain plays a rôle in the regulation of the numbers of circulating erythrocytes. They further stated that a humoral or endocrine intervening mechanism is not impossible. Hecht and Weil[7] found that concussion of the brain was at times accompanied by polycythemia.

Lichtwitz[8] reported a case of encephalitis with polycythemia and also a case of acromegaly with polycythemia.

A familial tendency toward polycythemia is not uncommon. Doll and Rothschild[9] reported a familial tendency toward polycythemia in conjunction with Huntington's chorea. Gutzeit[10] reported cases of polycythemia in two sisters and also in a patient who had a son suffering from lymphatic leukemia. Klumpp and Hertig[11] reported cases presenting a composite picture of both polycythemia and myelogenous leukemia.

Engelking[12] found eleven cases of the Vaquez form of polycythemia in three generations of one family. Tancré[13] also reported a familial tendency toward this condition.

Polycythemia with narcolepsy is not infrequent, as mentioned by Neisser,[14] Munzer,[14] Kraus[14] and Jolly.[14]

We have a case under observation at the present time. The relationship of the pituitary and the third ventricle area to narcolepsy has been frequently emphasized (Fulton and Bailey[15]). It is not surprising,

6. Schulhof, K., and Matthies, M. M.: Polyglobulia Induced by Cerebral Lesions, J. A. M. A. **89**:2093 (Dec. 17) 1927.

7. Hecht, P., and Weil, P.: Polycythämie und Hirnerschütterung, Aerztl. Sachverst.-Ztg. **35**:35, 1929; Deutsche med. Wchnschr. **55**:380, 1929.

8. Lichtwitz, L.: Hypophysäre Symptome und Hypophysenkrankheiten, Verhandl. d. deutsch. Gesellsch. f. inn. Med. (Kong. 42) 1930, p. 35.

9. Doll, H., and Rothschild, K.: Familiäres Auftreten von Polycythämia rubra im Verbindung mit Chorea progressiva hereditaria Huntington, Klin. Wchnschr. **52**: 2580, 1922.

10. Gutzeit, K.: Zur Pathologie und Genese der Polycythemia rubra, Deutsches Arch. f. klin. Med. **141**:30, 1922.

11. Klumpp, T. G., and Hertig, A. T.: Erythremia and Myelogenous Leukemia, Am. J. M. Sc. **183**:201, 1932.

12. Engelking, E.: Ueber familiäre Polycythemia, Klin. Monatsbl. f. Augenh. **64**: 645, 1920.

13. Tancré, E.: Zur Polycythemia rubra, Deutsches Arch. f. klin. Med. **123**: 435, 1917.

14. Quoted by Günther.[2]

15. Fulton, J. F., and Bailey, P.: Tumors in Region of Third Ventricle: Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1 (Jan.); 145 (Feb.); 261 (March) 1929.

therefore, that polycythemia is found in this condition if the pituitary is a factor in erythrocyte formation.

Recently Houssay, Royer and Orias [16] found that in sixteen hypophysectomized rabbits the average hemoglobin content in 100 cc. of blood equaled 11.56 Gm., whereas twelve normal rabbits had an average hemoglobin content of 13.6 Gm. The red cells were also diminished in the hypophysectomized animals, but the authors called attention to the marked variation in the red cell count of normal animals. Collin and Baudot,[17] from their work on the guinea-pig, concluded that the embryonic pituitary has a hematopoietic function. Watrin,[18] from his studies, believes that there are erythropoietic centers in the pituitary of the pregnant guinea-pig.

Moldawsky [19] believes that glandular disturbances produce stimulation of bone marrow, and that there is a constant hormone present in the blood stream which excites this stimulation. He cited various endocrine disturbances to prove this. He based his conclusions on eighty patients suffering from various endocrine diseases, such as exophthalmic goiter, myxedema, tumors of the pituitary, acromegaly and pituitary dystrophy. In order to keep the red cells constant, he said, there must be a hormone present which stimulates the formation of blood. He did not believe that any one gland specifically stimulates the red bone marrow but thought that the stimulation is the result of various hormones. He concluded that the red cells give an indication as to the function of the whole endocrine chain.

Falta, Bertelli and Schweeger,[20] giving posterior lobe extract by the hypodermic method, found an enormous and long-standing increase of hemoglobin and erythrocytes, later followed by a decrease.

Polycythemia associated with tumors of the suprarenal is not uncommon, and it is our contention that the polycythemia in these cases is really of pituitary origin, as shown by our experiments and clinical cases.

Zucker [21] reported a case of tumor of the suprarenal cortex in a woman, 35 years old, with polycythemia. Postmortem examination

16. Houssay, B. A.; Royer, M., and Orias, O.: Hemoglobina y globulos rojos en los perros hipofisoprivos, Rev. Soc. argent. de biol. **7**:314, 1931.

17. Collin, R., and Baudot, J.: Erythropoïese dans l'hypophyse, Compt. rend. Soc. de biol. **86**:596, 1922.

18. Watrin, J.: Foyers d'erythropoïese dans l'hypophyse de cobaye gravide, Compt. rend. Soc. de biol. **87**:558, 1922.

19. Moldawsky, J. W.: Ueber die Regulierung der Konstanz des roten Blutes, Ztschr. f. klin. Med. **114**:346, 1930.

20. Falta, W.: Bertelli, and Schweeger: Ueber Beziehungen der inneren Sekretion zum Salzstoffwechsel, Verhandl. der Kong. f. inn. Med., Wiesbaden, 1909, p. 138.

21. Zucker, E.: Maligner Nebennierenrindentumor mit Virilismus und Polycythämie, Wien. klin. Wchnschr. **42**:1045, 1929.

revealed carcinoma of the left suprarenal cortex, pulmonary metastasis, an enlarged spleen, an atrophic right suprarenal and a large left cardiac ventricle. No gross thyroid or pituitary change was found. This case, as well as others, shows the importance of making microscopic sections of the pituitary. Cushing [1] stressed the importance of this in his article on pituitary basophilism.

Redlich [22] reported the case of an 18 year old youth suffering from impotence, polyuria and obesity, who had a hypernephroma of the right suprarenal and atrophy of the left suprarenal. There was no polycythemia. The pituitary was markedly atrophic, weighing but 0.25 Gm. as compared with the average normal weight of 0.63 Gm.

Schlüter [23] described a case of hypernephroma of a 33 year old woman who had had amenorrhea for five years. The tumor was derived from the suprarenal cortex. The pituitary showed an increase in the eosinophilic cells with some decrease of basophil cells. Hypertension was also present. The ovaries were atrophic and fibrotic.

That the suprarenal is thought to have something to do with red cell formation is the opinion of several workers, but it is our contention that this is a specific pituitary function.

Schweizer [24] believes that the suprarenals influence centers which have a hematopoietic influence. If the suprarenals are defective, the central regulating mechanism is defective. He bases this conclusion in part on the observation of defects of the brain associated with suprarenal defects.

Huth [25] gave suprarenal cortex extract to patients suffering from various diseases, and seventeen of twenty-six cases showed a marked increase of red blood cells.

Pal [26] obtained excellent results with suprarenal cortex extract in various diseases (with respect to the red cell count). In pernicious anemia positive results were also recorded.

Soos [27] believes that in degeneration and necrosis of the suprarenal cortex, a toxin is formed which stimulates bone marrow. He thinks

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22. Redlich, F.: Pluriglanduläre Störungen bei einem Fall von Hypernephrom, Med. Klin. **26**:1255 (Aug. 22) 1930.

23. Schlüter, A.: Hypernephroma-like Tumor of Left Suprarenal With Metastases to the Liver and Aplasia of the Right Suprarenal, Frankfurt. Ztschr. f. Path. **40**:97, 1930.

24. Schweizer, R.: Die Nebenniere als Kontrollorgan für die Blutkonstanz, Schweiz. med. Wchnschr. **8**:633, 1927.

25. Huth, E.: Ueber die Wirkung der Nebennierenrinde und des Histamins auf die Blutregeneration, Wien. klin. Wchnschr. **42**:729, 1929.

26. Pal, J.: Medical Furtherance of the Formation of Red Blood Cells, Med. Klin. **24**:1071, 1928.

27. Soos, J.: Ueber die Korrelation der Epithelien und der Nebennieren im Lichte der Untersuchungen der Knochenmarksherde der Nebennieren, Beitr. z. path. Anat. u. z. allg. Path. **86**:444, 1931.

that there is a close relationship between the suprarenal cortex cells and the reticulo-endothelial system.

Several workers found polycythemia after extirpation of the adrenals in animals.

Szymonowicz [28] found polycythemia after this procedure. Gradinescu [29] noted an increase of erythrocytes, averaging 28.5 per cent in dogs and 72 per cent in cats. Dale [30] observed a concentration of the blood elements as did Donath.[31]

Kellaway and Cowell [32] found an increase of hemoglobin and erythrocytes after extirpation of the suprarenals. They believe that the changes in the concentration of the blood are dependent only on the damage to the suprarenal cortex.

Stewart and Rogoff [33] did not find a constant change in the erythrocyte count; the relative increase of the serum was usually found on the day of death or just preceding it.

Bazett [34] found a lessening of the blood volume and erythrocytes after adrenalectomy.

Pende [35] noted a slight decrease of the erythrocytes and hemoglobin in young animals after adrenalectomy.

Polycythemia in Addison's disease is not rare. Rowntree and Snell [36] found polycythemia in Addison's disease. In one hundred and eight cases the erythrocyte count ranged from 6,000,000 to 6,400,000 in one, from 5,000,000 to 5,400,000 in sixteen and from 4,500,000 to 4,900,000 in forty-three. Twenty-two had hemoglobin values ranging from 80 to 89 per cent and three values from 90 to 99 per cent. The average hemoglobin value in the one hundred and eight cases was 74.7

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28. Szymonowicz, L.: Die Funktion der Nebennieren, Arch. f. d. ges. Physiol. **64**:97, 1896.

29. Gradinescu, A. V.: Der Einfluss der Nebennieren auf den Blutkreislauf und den Stoffwechsel, Arch. f. d. ges. Physiol. **152**:187, 1913.

30. Dale, H. H.: Conditions Which Are Conducive to the Production of Shock by Histamine, Brit. J. Exper. Path. **1**:103, 1920.

31. Donath, quoted by Ehrmann, R., and Dinkin, L., in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch. 1928, vol. 3, p. 283.

32. Kellaway, C. H., and Cowell, S. J.: On the Concentration of the Blood and the Effects of Histamine in Adrenal Insufficiency, J. Physiol. **57**:82, 1923.

33. Stewart, G. N., and Rogoff, J., quoted by Bayer, G., in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1928, vol. 2, p. 752.

34. Bazett, H. C.: Time Relations of Blood Pressure Changes after Excision of Adrenal Glands, With Some Observations on Blood Volume Changes, J. Physiol. **53**:320 (Feb. 20) 1920.

35. Pende, N.: Endocrinologia: Patologia e clinica degli organi a secrezione interna, Milan, Francisco Vallardi, 1913.

36. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

per cent, and the average erythrocyte count was 4,550,000. The authors said that anemia, in the restricted sense of the word that is now in vogue, is not common in Addison's disease.

The volume of the blood and plasma is usually normal in Addison's disease, except during the crises and terminal phases, according to these writers.

The value of the observations made on such a large series is obvious.

Polycythemia in Addison's disease was noted by early writers (Acuna,[37] Bramwell,[38] Christomanos,[39] Leva,[40] Rombach,[41] Vollbracht[42] and von Willebrand[43]). Of four cases of Addison's disease coming to autopsy at Harper Hospital since 1920, two showed polycythemia; unfortunately, reports on the pituitaries are not available.

RELATION BETWEEN SUPRARENAL CORTEX AND PITUITARY GLAND

From all of the available data, both clinical and experimental, which we possess, we are safe in saying that aplasia and hypoplasia of the pituitary are accompanied by aplasia and hypoplasia of the suprarenal cortex, whereas the reverse is found in hyperplasia of the pituitary. One of us (Dr. Moehlig[44]) has discussed this relationship elsewhere. As Kraus[45] said, anomalies of the pituitary are most frequently found in anencephalia, hydrocephalus and other cerebral developmental anomalies. It has long been observed by older pathologists that when the anterior part of the brain is defective, aplasia of the suprarenal cortex and other developmental defects of this portion of the suprarenal

37. Acuna, M.: Enfermedad de Addison con hiperglobulia, Arch. latino-am. de pediat., 1905, cited in Folia haemat. **3**:101, 1906.

38. Bramwell, B.: A Case of Addison's Disease in Which a Great Improvement Took Place Under Open Air Treatment and Administration of Suprarenal Extract, Brit. M. J. **2**:1082, 1905.

39. Christomanos, Anton: Ueber die Zahl der roten Blutkörperchen in zwei Fällen von Nebennierenerkrankung, Berl. klin. Wchnschr. **36**:916, 1899.

40. Leva, J.: Zur Lehre von Morbus addisonii, Virchows Arch. f. path. Anat. **125**:35, 1891.

41. Rombach, K. F.: Morbus addisonii mit Polycythämie und Miltztumor, Tijdschr. v. diergeneesk. **1**:425, 1907.

42. Vollbracht, F.: Fall von Morbus addisonii nach vorangegangener Purpura haemorrhagica mit einer Stoffwechseluntersuchung, Wien. klin. Wchnschr., 1899, p. 737.

43. von Willebrand: Handlung Morbus addisonii mit Atrophie der Nebennieren, Finska läk.-sällsk. handl. **47**:536, 1905.

44. Moehlig, R. C.: The Pituitary Gland and the Suprarenal Cortex, Arch. Int. Med. **44**:339 (Sept.) 1929.

45. Kraus, E. J.: Die Entwicklungsstörungen der Hypophyse, in Gruber, G. B.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1929, vol. 3, p. 483.

were present. We now know that this is due to primary pituitary involvement. Smith,[46] Evans [47] and others have shown that hypophysectomy results in atrophy of the suprarenal cortex.

Hyperplasia of the pituitary is accompanied by hyperplasia of the suprarenal cortex, as illustrated by experimental and clinical data.[44] Putnam, Benedict and Teel,[48] Smith,[46] Evans,[47] Hofstätter,[49] Houssay,[50] Moehlig and Osius [51] and many others have been able to produce hypertrophy of the suprarenal cortex by injections of pituitary extract. In hyperpituitarism we usually find hyperplasia of the suprarenal cortex. This is true of the Cushing syndrome, described previously.

Briefly, the suprarenal cortex reflects the state of the pituitary gland.

Primary disease of the suprarenal cortex, resulting in either a hypofunction or hyperfunction, is accompanied by a variable, but nevertheless definite, secondary change in the pituitary. We believe that this secondary change of the pituitary in response to primary disease of the suprarenal cortex explains many symptoms erroneously attributed to the suprarenal cortex. Those persons predisposed to deficiency of the suprarenal cortex, for instance, constitutionally possess, as Kraus [52] has shown, a hypoplastic pituitary, so that the response of the latter is not as marked as those possessing a normal or hyperplastic pituitary. It is to be emphasized, however, that there is, on the whole, some pituitary response to primary suprarenal deficiency even though the pituitary is hypoplastic.

In normal dogs possessing a normal pituitary, if one produces an acute adrenal insufficiency by bilateral adrenalectomy the pituitary is able to respond by hyperplasia, and polycythemia results.

Clinically, at least, the general rule is that primary suprarenal insufficiency is accompanied by pituitary insufficiency. It reverts, there-

46. Smith, P. E.: Disabilities Caused by Hypophysectomy and Their Repair; Tuberal (Hypothalamic) Syndrome in the Rat, J. A. M. A. **88**:158 (Jan. 5) 1927.

47. Evans, H.: Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1923-1924.

48. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly, Arch. Surg. **18**:774 (April) 1929.

49. Hofstätter, R.: Ueber Befunde bei hyperhypophysierten Tieren, Monatschr. f. Geburtsh. u. Gynäk. **19**:387, 1919.

50. Houssay, B.: Estudios sobre la acción de los extractos hipofisianos: Ensayos sobre la fisiología de lobulo posterior de la hipofisis, Buenos Aires, A. Guidi Buffarini, 1911.

51. Moehlig, R. C., and Osius, E.: The Pituitary Factor in Arteriosclerosis, Ann. Int. Med. **4**:578, 1930.

52. Kraus, E. J., and Traube, O.: Ueber die Bedeutung der basophilen Zellen der menschlichen Hypophyse, Virchows Arch. f. path. Anat. **268**:315, 1928. Kraus, E.: Zur Pathologie des Morbus addisonii (Befunde in Hypophyse und Nebennieren), Beitr. z. path. Anat. u. z. allg. Path. **78**:283, 1927.

fore, to the constitutional make-up of the patient, in that he either does or does not congenitally possess an active pituitary gland.

Substantial proof of this is offered by the work of Kraus and his associates. Kraus and Traube [52] examined two hundred and thirty-two pituitaries of persons who had been ill but a short time, so that no change in the pituitary would be expected from the illness. Another group was obtained from persons who had either died by accident or had committed suicide. The conclusions arrived at were as follows:

1. The most important findings in our systematic examination of two hundred and thirty-two cases in which the basophil cells were studied give the following results: Normal people of medium build (mesosthenic habitus), normal development and nutrition show, on the whole, a constant number of basophil cells in the anterior lobe, which we designate in our work as X X X.

2. Normal persons of hypersthenic habitus show, as a rule, a marked increase of the basophil cells as compared with those of the healthy mesosthenic habitus.

3. Persons with diseases which attack, as a rule, the hypersthenic type, such as essential hypertension, vascular sclerosis, contracted kidneys, constitutional obesity and, in a certain degree, chronic alcoholism, progressive paralysis and aortitis of syphilitic origin, show a very high percentage of basophil cells and a marked increase of the basophil cells as compared with the mesosthenic type.

4. Persons with high blood pressure, chronic nephritis and so-called secondary contracted kidneys also have a marked increase of the basophil cells as compared with the normal mesothenic type.

5. Asthenic persons, such as the diabetic and tuberculous types, in whom the blood pressure is low show a diminution of the basophil cells in a majority of cases. Persons with cancer cachexia who have hypotension show a diminution of the basophil cells.

6. Persons with disturbances of the suprarenals or with marked hypoplasia or atrophic suprarenals, particularly of the addisonian type, show in the majority of cases a distinct diminution of the basophil cells.

7. As to the relationship between the basophil cells of the pituitary and the suprarenals, 72.7 per cent of the persons with suprarenals rich in lipoid (12 Gm. or more) show a marked increase of the basophil cells.

8. Our studies on these two hundred and thirty-two pituitaries taken from normal and sick persons permit the conclusion that there is a definite relationship between the basophil cells of the pituitary and the constitutional type of the patient; likewise between these and the blood pressure as well as the state of the suprarenals. In other words, there is a definite relationship between the basophil cells, the constitutional make-up of the patient, the blood pressure and the size of the suprarenals.

9. There is, apparently, also a relationship between the basophil cells of the pituitary, the cholesterol content of the blood and the suprarenals. This is important because of the relationship between the cholesterol content of the blood and vascular disturbances.

10. Concerning the relationship between the number of the basophil cells of the pituitary and changes in the thyroid, thymus and sex glands, particularly the ovaries, we may not draw any definite conclusions.

We see, therefore, that the state of the pituitary is reflected in the suprarenal cortex. The constitutional type of the patient, the size of the suprarenal cortex, the blood cholesterol value and the number of pituitary basophils parallel one another.

As further confirmation of Kraus' work, Mjassinikow [53] found that hypersthenic persons have a blood cholesterol value of 1.8, whereas those of the asthenic type show a definite decrease, the cholesterol value being 1.3. Kraus believes, therefore, that there is a definite parallelism between the cholesterol content of the blood and the basophil cells.

Without entering into a consideration of hypertension, it is interesting that the syndrome described by Cushing usually includes hypertension. The relationship between the cholesterol metabolism, suprarenal cortex, hypertension and pituitary basophils is important. Berblinger [54] found that the basophil cells extend into the posterior lobe, from which comes the blood pressure-raising principle.

Moehlig and Osius [51] fed rabbits for one hundred days on a diet of high cholesterol content and injected daily doses of posterior lobe extract; this produced, among other things, an intense arteriosclerosis and marked hyperplasia of the adrenal cortex. It is possible that the basophil cells of the anterior lobe may furnish the "mother" substance to the posterior lobe, as would be suspected from Berblinger's histologic studies.

Zondek [55] expressed the opinion that this is the reason why posterior lobe extract at times produces the same results and reactions as his anterior lobe substance.

Kraus [52] reported on the changes in the pituitary in four cases of Addison's disease. Three of the four cases showed regressive changes in the basophil cells of the pituitary, whereas in the fourth case no particular change was found in this gland. In the three cases with changes, the basophil cells showed a varying degree of granulation loss, massing together of the cells and a marked diminution in the number of cells.

Of six additional cases of suprarenal atrophy, four showed typical Addison's disease. In another case of Addison's disease the basophil cells were diminished to a slight degree, showing a weak granulation and no great changes. In those cases in which the pituitary does not regenerate, there follows atrophy of the cells with thinning of the connective tissue; if regeneration does set in, either a new formation of chief cells or small chromophobe cells ensues or there may be some granulation of

53. Mjassinikow, A. L.: Beiträge zur Konstitutionsforschung; Blutcholesteringehalt und Konstitution, Ztschr.f. klin. Med. **105**:228, 1927.

54. Berblinger, W., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

55. Zondek, B.: Arch. f. Gynäk. **144**:491 (Oct.) 1931.

the basophils with deeper staining qualities. Rarely do there follow full-fledged basophil cells.

Kiyono [56] reported two cases of Addison's disease. The first patient had tuberculosis of the suprarenals and the pituitary was small; the anterior lobe was hyperemic, the basophils were reduced and diminished pigment was present in the posterior lobe. The second case was associated with otitis media. The weight of the pituitary was 0.5 Gm. The anterior lobe was hyperemic, the eosinophils were not lessened and stained deeply, a colloid cyst was present in the pars intermedia and the posterior lobe contained no pigment.

Berblinger [57] cited a case of Addison's disease in a 7 year old boy with a high grade suprarenal hypoplasia in which the pituitary showed no characteristic changes. His other case of Addison's disease was due to a caseous degeneration of the suprarenals, and the pituitary showed a lessening of the chromophils. He gave as his opinion that this represents suprarenal insufficiency only and not a complete *Organ Ausfall*, and therefore this will influence the extent of the pituitary reaction. Whether, Berblinger said, the basophils deliver a different secretion than the eosinophils is as yet unsettled.

Harrop and Weinstein [58] reported a case of Addison's disease in which hypoplasia of the basophils of the anterior lobe was found.

We observed the following case:

S. B., a white man, aged 51, an American, entered Harper Hospital on Jan. 19, 1932, complaining of loss of weight and strength, gastric disturbances, pain and swelling of the right knee and easy fatigue for about two years.

In October, 1927, while in good health, he began to have a constant dull aching pain and soreness in the right flank which developed suddenly, independent of trauma or other symptoms. It continued without radiation and without urinary disturbances up to the time of admission, but in a milder form. In April, 1930, trauma to the right knee resulted in a painful reddened swelling which has persisted with exacerbations up to the present time. It remained swollen and tender and developed a brawny color. In January, 1931, he noticed he was losing weight and strength. In October, 1930, he weighed 245 pounds (111.1 Kg.), and in June, 1931, nine months later, he weighed only 137 pounds (62.1 Kg.). By April, 1931, the weakness and fatigability had become so marked he had to give up all activity. In June a severe gastric upset with nausea and vomiting, but without jaundice, caused his physician to prescribe for liver trouble, and on this regimen he remained fairly comfortable until November 1. During this period a yellowish tint to the skin developed, and brownish pigmented spots appeared on the skin of the abdomen, chest, face and arms. After November, the patient began

56. Kiyono, H.: Histopathologie der Hypophyse, Virchows Arch. f. path. Anat. **259**:388, 1926.

57. Berblinger, W.: Die korrelativen Veränderungen an der Hypophyse des Menschen, Klin. Wchnschr. **7**:9 (Jan. 1) 1928.

58. Harrop, G. A., and Weinstein, A.: Addison's Disease Treated with Suprarenal Cortical Hormone (Swingle-Pfiffner), J. A. M. A. **98**:1525 (April 30) 1932.

to lose more weight and strength, his knee gave him much discomfort and he had several severe attacks of vomiting.

There was never any blood in the vomitus or any bloody or tarry stools. No history of alcoholism was obtained. The only past illness was malaria in 1908. At the age of 20, following an injury while working in a coal mine, he had gross hematuria for a week.

His father died of pneumonia; his mother, six brothers and three sisters were living and well. Two brothers died in infancy, and one was killed in an accident. Two sisters died of acute infectious disease. There was no family history of tuberculosis.

The patient had been married twenty-nine years. His wife and two children were living and well; three children died in infancy of intestinal disease.

Examination disclosed a well developed but poorly nourished man of 51 years, alert and cooperative. The skin of the face and neck was plethoric and showed a brownish discoloration over the chest, arms and abdomen. The mucous membrane of the mouth under both upper and lower plates was pigmented. The heart sounds were distant. The heart was of normal size. The blood pressure was 122 systolic and 80 diastolic; the pulse rate was 78. The peripheral arteries were compressed with difficulty. Diminished breath sounds only were found in the lungs, resonance being unimpaired. The right knee was swollen, reddish brown and tender. Active and passive movements were painful and flexion greatly limited. There was moderate tenderness deep in the right flank. The liver and spleen were just palpable. The urine was normal. The hemoglobin content was 94 per cent. The red blood cells numbered 6,510,000; the white blood cells, 9,100. The differential count showed: polymorphonuclears, 52 per cent; small lymphocytes, 34; large lymphocytes, 10, and eosinophils, 4. Subsequent counts were essentially the same.

Roentgen examination disclosed a destructive process in the right knee joint, probably tuberculous, and a bilateral parenchymal involvement of the upper lobe, with a lobular distribution of tuberculous origin. After examining the skull the roentgen department reported: "There is slight depression of the floor of the sella, which would indicate some pituitary enlargement. There is no evidence of erosion of either the anterior or the posterior clinoids. The pineal gland shows calcification, which is normal for adult life."

The urine showed no sugar at any examination. Tests for dextrose and levulose tolerance and the bromsulphalein tests gave results within normal limits.

The diagnosis was: Addison's disease, tuberculosis of the right knee joint and polycythemia.

The patient's course in the hospital was definitely downward, with severe gastro-intestinal upsets, lowered blood pressure and finally coma and death, fourteen days after admission. Permission for postmortem examination could not be obtained, but we may safely assume that there was a destruction of the suprarenal glands by a tuberculous process.

We believe that this man originally possessed a very active pituitary gland and was able to respond with a polycythemia and marked pigmentation.

Bell [59] reported a case which he diagnosed as Addison's disease associated with acromegaly. Unfortunately no autopsy was performed;

59. Bell, B.: The Pituitary, New York, William Wood & Company, 1919.

this would have been enlightening for several reasons. Hyperplasia of the pituitary is usually associated with hyperplasia of the suprarenal cortex. This case of Bell's is unusual, therefore, unless we postulate a primary hypoplasia of the suprarenal cortex with secondary hyperplasia of the pituitary gland.

The state of the pituitary after extirpation of the adrenals in animals has been reported on by few workers. Boinet [60] and Marenghi [60] found hyperfunction of the pituitary after extirpation of the adrenals. Bell [59] found hypertrophy of the middle lobe, whereas Alquier [60] and Pende [60] found no changes. Urechia and Mihalescu [61] found enlargement and congestion of the anterior pituitary and a definite increase of the cosinophils. Boyd [62] said that removal of most of the adrenal tissue is followed by pituitary hyperplasia.

Poos,[63] using various animals in a large series of experiments, concluded that the pituitary always reacts qualitatively in the same way when other glands of internal secretion are disturbed by experimental attack. The quantitative differences are dependent on the severity of the endocrine changes produced and, secondarily, on the length of the experiment. He differentiated four stages of reaction processes affecting the pituitary after adrenalectomy: (1) the stage of increased physiologic reaction, (2) the stage of pituitary hydrops, (3) the stage of degeneration and (4) the stage of pigment formation.

He expressed the opinion that the pituitary is influenced by general metabolic disturbances and that this metabolic stimulus always results in a qualitative change in this gland. The quantitative change, he said, is dependent on the severity of the endocrine changes produced and, secondarily, on the length of the experiment.

Lehmann's [64] experiments on rats concerned the reaction of the pituitary after ablation of the adrenals. Soon after extirpation of both adrenals, the hair became brittle, even in the young animals, and finally fell out, particularly in the region of the back. In some animals, black hair became lighter and there was some lessening of the epidermal pigment. The adenohypophysis showed a diminution of cosinophils. The

60. Quoted by Bayer, G., in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1928, vol. 2, pt. 3, p. 752.

61. Urechia, C. I., and Mihalescu, S.: Histologic Study of Tuber Cinereum and Nuclei of Base in Acute Operative Insufficiency of Suprarenals, Rev. franç. d'endocrinol. **3**:296 (Oct.) 1925.

62. Boyd, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931.

63. Poos, F.: Genese und Deutung der Reaktionsformen der Hypophysis cerebri, Ztschr. f. d. ges. exper. Med. **54**:709, 1927.

64. Lehmann, J.: Die Struktur des Hirnanhanges nebennierenloser Ratten, Ztschr. f. d. ges. exper. Med. **65**:129, 1929.

pars intermedia did not show any particular change. The pars nervosa showed a high grade edema, particularly at the base of the posterior lobe. Lehmann found that the pigment disappeared rapidly in the pars intermedia and never returned.

Berblinger [57] took exception to some of Poos' conclusions. He expressed the belief that the nature and reactions of glandular secretions are specific and are not really due to a general metabolic change. Furthermore, Berblinger said that if one studies the reactions of the pituitary of the human subject, not only in pregnancy but in athyreosis and hypothyroidism, he will find quantitative differences. As illustrative of the latter reaction he considered hypertrophy of the chief cells of the pituitary in cancer with hepatic metastasis; also in two cases of multiple myeloma. However, these pituitary changes do not occur constantly in cases of neoplasm other than in association with athyreosis or hypothyroidism.

Concerning the production of the Cushing syndrome due to pituitary basophilism and also pituitary disturbances in general, a logical explanation is found in the embryohormonic relations of the pituitary to mesodermal tissues. This relationship was shown originally by one of us (Dr. Moehlig [65]) in 1914, and since then the principle outlined has gained some acceptance (Cushing and Davidoff,[66] Putnam,[67] Brugsch [68] and Hofbauer [69]).

For clearness, the mesodermal tissues are given as follows:

1. Connective tissue (all types of connective and supporting tissues)
2. Cutis or corium, including the hair papillae
3. Cartilage; bone
4. Dentin and cementin of the teeth
5. Pigment cells, mesodermal
6. Lymph glands; lymphatics; lymph cells } Reticulo-endothelial system
7. Spleen
8. Blood
9. Blood vessels
10. Fat cells

65. Moehlig, R. C.: A Study of the Ductless Glands, Detroit M. J. **14**:268, 1914

66. Cushing, H., and Davidoff, L.: Studies in Acromegaly: V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, New York, Rockefeller Institute for Medical Research, 1927, monograph no. 22.

67. Putnam, T.: Separation of Growth-Producing Hormone from That Inducing Premature Estrus in the Anterior Pituitary Gland, Arch. Surg. **18**:765 (April) 1929.

68. Brugsch, T.: Lehrbuch der inneren Medizin, Berlin, Urban & Schwarzenberg, 1930, vol. I, p. 141.

69. Hofbauer, J.: Ueber Beziehungen des Hypophysenvorderlappens zum Uteruscarcinom, Klin. Wchnschr. **9**:2153 (Nov. 14) 1930.

11. Smooth muscle (with exception of the iris musculature)
12. Renal cells
13. Nerve and corpuscles
14. Joint cavities; bursae; subarachnoid and subdural spaces and their linings
15. Suprarenal cortex

(*a*) Pleurae, peritoneum and pericardium
(*b*) Sex glands and tissues
(*c*) Skeletal muscle, including the specialized cardiac muscle
} Mesothelium

The suprarenal cortex controls the mesothelial tissues cited. This embryohormonic relationship has been discussed elsewhere.[70] It is apparent that the pituitary could influence and control these tissues as well.

Cushing [1] said:

> While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal or with adrenal tumors, the fact that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior pituitary for lesions of similar composition.

It is our opinion, however, that the majority of symptoms characterizing this syndrome are always due to involvement, either primarily or secondarily of the pituitary, regardless of which endocrine gland is primarily involved.

From the metabolic standpoint it is certain that hyperglycemia with glycosuria is frequently found in pituitary disturbances. Houssay [71] and his associates have contributed much to our knowledge on the importance of the pituitary in carbohydrate metabolism. They believe that the pituitary is the most important regulating factor in carbohydrate metabolism. From this we can also infer that the hypoglycemia usually present in atrophic conditions of the suprarenal cortex, such as seen in Addison's disease, is really due to *failure of the pituitary function*

70. Moehlig, R. C.: (*a*) Ductless Gland Cell Control, Monograph (privately printed), 1918; (*b*) Selective Action of the Suprarenal Cortex on Mesothelial Tissues, Am. J. M. Sc. **168**:553, 1924; (*c*) Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues, Ann. Int. Med. **1**:828, 1928; (*d*) J. Lab. & Clin. Med. **16**:118, 1930; (*e*) footnote 45; (*f*) footnote 65; (*g*) Moehlig, R. C., and Ainslee, H. B.: Pituitary Gland and Cholesterol Metabolism, Ann. Clin. Med. **5**:772, 1927; (*h*) Posterior Pituitary Extract and Cholesterol Metabolism, Am. J. Physiol. **80**:649, 1927.

71. Houssay, B. A.: Die funktionellen Beziehungen zwischen der Hypophyse und dem Pankreas, Endokrinologie **5**:103, 1929. Houssay, B., and Biasotti, A.: Pankreasdiabetes und Hypophyse beim Hund, Arch. f. d. ges. Physiol. **227**:664, 1931; Hypophysektomie und Pancreasdiabetes bei der Kröte, ibid. **227**:239, 1931.

and not to the suprarenal cortex.[71a] This is well illustrated in pituitary cachexia in which hypoglycemia is pronounced.

Then too, the influence which this gland has on cholesterol metabolism by affecting the mesodermal fat cells and suprarenal cortex is gaining recognition and accounts for the hypercholesteremia.

Kraus,[72] Smith,[72] Raab,[73] Anselmino and Hoffmann,[74] Mjassinikow[75] and Moehlig and Ainslee[76a,b] have shown the influence which the pituitary has on fat metabolism.

Disturbances of cholesterol are associated with hypertension, diabetes mellitus, nephritis, arteriosclerosis and several other conditions.

In the article by Moehlig and Ainslee,[76a] some of the points made are of interest in regard to the syndrome under discussion. They said: "Furthermore, the pituitary supposedly has an erythropoietic function. In hyperpituitarism, polycythemia with an increased blood volume is present and in hypopituitarism, anemia with a lessened blood volume is present." Part of the summary was: "The pituitary gland, regulating the suprarenal cortex and other mesodermal tissues, plays an important rôle in the pathogenesis of diseases associated with abnormalities of cholesterol metabolism. Such diverse clinical entities as atherosclerosis, hypertension, certain types of nephritis, disturbances in the volume of blood, cholelithiasis, diabetes and uterine fibroids are found to have important relations to states of pituitary hyperfunction and exhaustion."

The hypertrichosis is a pituitary and not a suprarenal symptom. As noted, the hair papilla with its nutritional element is a mesodermal tissue, so that the pituitary overactivity results in stimulation of the hair papillae. Persons with hypersthenic, acromegalic, pituitary, basophilic and hyperpituitary states in general have marked hirsutism. The recent work of Bengtson,[75] as well as that of earlier workers,[76] has shown the influence of the pituitary on the growth of the hair. Hypophysectomy in dogs results in permanent lanugo formation.[76]

The hypertrichosis of persons with ovarian tumors is also, we believe, of pituitary origin.

71a. This should be qualified in that the suprarenal cortex influences the skeletal muscle metabolism.

72. Smith, P. E.: Disorders Induced by Injury to the Pituitary and the Hypothalamus, J. Nerv. & Ment. Dis. **74**:50, 1931.

73. Raab, W.: Rôle of Pituitary Posterior Hormone in Fat Metabolism, Endocrinology **14**:385 (Nov.-Dec.) 1930.

74. Anselmino, K. J., and Hoffmann, F.: Fat Metabolism Hormone of Anterior Lobe of Hypophysis, Klin. Wchnschr. **10**:2380 (Dec. 26) 1931.

75. Bengston, B.: Pituitary Therapy of Alopecia, J. A. M. A. **97**:1355 (Nov. 7) 1931.

76. Aschner, B., in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1928, vol. 2, p. 354.

Briefly, the development of the hair is always a result of pituitary activity, regardless of which endocrine gland is involved.

This specific influence of the pituitary on mesodermal tissues provides a much better understanding of the hypertrichosis seen in suprarenal and ovarian disturbances, which is due to secondary involvement of the pituitary.

Polycythemia is, no doubt, the result of the pituitary influence on the mesodermal reticulo-endothelial system. If we study the influence of the pituitary on growth, it is reasonable to assume that the important hematopoietic system should be stimulated to activity by its secretion. The mesodermal bone tissue, spleen, reticulo-endothelial system of the liver, etc., are known to be influenced by the state of the pituitary. It is well known that in hyperpituitary states, such as that seen in pituitary eosinophilism or acromegaly, the whole hematopoietic system becomes hyperplastic. The relationship of the pituitary to cholesterol metabolism, previously discussed, is of importance in regard to the protective influence of cholesterol on erythrocytes.

The pigmentation which so often accompanies hyperpituitary conditions may be due to the influence of the pituitary on the mesodermal pigment cells. We cannot, of course, here consider the vast field of pigmentation, but if pigment formation is a metabolic phenomenon, the mesodermal origin of all pigment is most likely. Such an assumption would give the pituitary a major rôle in pigmentation. What we would like to suggest is that the pituitary is concerned in the production of addisonian pigmentation. At present we have been bound by convention to believe that the suprarenals are the only responsible factors.

Certain clinicopathologic data are of great importance in this discussion:

1. Hyperpituitary conditions, such as acromegaly and basophilism, are usually found in dark-haired, dark-complexioned, hypertrichotic persons.

2. Hyperfunctioning suprarenal cortex tumors are also found in this same type and, as our cases suggest, the pituitary becomes hyperplastic in these conditions.

3. In pituitary cachexia (Simmond's disease), representing an extensive degree of pituitary atrophy or destruction, there is present a hypoplasia of the suprarenal cortex of a degree comparable with that seen in Addison's disease; yet we find no pigmentation. The patients have asthenia and a low blood pressure, which is also comparable with that seen in Addison's disease. In our case, in a girl of 15 years, pituitary cachexia developed, with marked decay of the teeth, falling out of the hair, amenorrhea, a loss of 102 pounds (46.2 Kg.) in nine

months, a blood pressure of 74 systolic and 60 diastolic and extreme asthenia. The patient was light in color and showed no pigmentation, owing, we believe, to the fact that the pituitary was primarily at fault. It is logical to assume that in these cases, in which the pituitary is primarily hypoplastic, it cannot respond to atrophy of the suprarenal cortex (which it causes) as in primary disease of the suprarenal cortex.

The amenorrhea, due, as has been shown, to atrophic and fibrotic ovaries, needs mention. This would seem to be an end-result of pituitary overactivity, in that the ripening mulberry stage has been followed by fibrosis and atrophy. It would be interesting to see the ovaries in an *early* stage of pituitary basophilism. Experimentally, as we know from Zondek's[77] work, hormonal sterilization may be produced by injections of anterior lobe substance. The whole ovary becomes a mass of corpus luteum, and amenorrhea results. It would seem that the fibrotic and atrophic ovary is the late result of this lutein stage. Clinically, we have seen comparatively young women of the dark-complexioned, hypertrichotic type, who give a history of menstruation beginning early in life (from 10 to 11 years of age), rather profuse and lasting from seven to ten days; this is followed in a few years by too frequent menstruation (twice a month) and, within a short time, by irregularity, skipping one or two months; finally there is complete amenorrhea.

We feel that this type duplicates the different stages of ovarian cellular activity in response to pituitary overactivity.

Our endeavor to show that the pituitary is really responsible for many signs and symptoms erroneously ascribed to the suprarenal cortex might lead one to believe that the function of the latter is a minor one. On the contrary, we feel that the suprarenal cortex, essential as it is to life, has definite relations to the mesothelial portion of the mesoderm. Its secretion is essential for the proper development and functioning of these tissues. This was emphasized in other papers.[70]

REPORT OF CASES

CASE 1.—Mrs. S., a housewife, 43 years old, entered Harper Hospital on June 11, 1931, complaining of nervousness and palpitation of the heart for eight years, multiple ecchymoses for four years, flushing of the face and intermittent pains in the joints for one year.

Her father was killed in an accident at the age of 70, but her mother is living and well at the age of 65. Both were short and stout, the mother being of the same build as the daughter, 5 feet (152.4 cm.) tall and weighing 138 pounds (62.6 Kg.). She is married and had one pregnancy terminating spontaneously at six months. Her menses began at the age of 14 years and were regular but too profuse. She did not menstruate after an operation for the removal of tumors of the womb nine years before the present examination; she thought that her

77. Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, Julius Springer, 1931.

ovaries were also removed at that time. Her tonsils were removed eleven years before. Four years before examination she had two operations on the sinuses, and in the same year bladder gravel was removed. All the teeth were extracted 3 years before. She has had no serious illnesses.

She was well for about a year following the removal of the fibroids and ovaries, and then (eight years before examination) she noticed the onset of nervousness, irritability and emotional outbursts. Associated with this were occasional periods of giddiness and palpitation, at times severe, which were ushered in without cause. This situation continued without change until about four years before, at which time she noticed huge ecchymoses making their appearance at irregular intervals, apparently without cause. The ecchymoses cleared readily and then appeared elsewhere, a brownish pigmentation remaining. About two or three years before, she noticed bright blood oozing from the skin at times, without finding any apparent bleeding point. At one time she bled from the forehead and again from the fingers. The bleeding always stopped spontaneously.

Fig. 1 (case 1).—Note the masculine appearance, marked hirsutism and prominent eyes.

Cuts and bruises, however, always healed normally. About one year before, she began to notice a peculiar flushing of the face accompanied by severe headaches of a throbbing character, especially over the left frontal and temporal areas. At these times, she said, her blood pressure was found to be as high as 230 systolic. Associated symptoms were dizziness, blurring of vision and the appearance of yellow spots before the eyes. About this time her skin became very dry, although she occasionally perspired, and she noticed an excessive growth of hair over the face and other parts of the body. Then fleeting multiple pains in the joints became troublesome, all the joints being involved at one time or another, although there was never any redness or swelling. During the later months, a peculiar crawling sensation gradually developed in the skin of the arms, then in the scalp and later all over the body. The patient's weight remained normal all through the illness, although weakness and fatigue became part of the picture.

To be noted on examination were the masculine facies, the plethoric appearance of the face, the prominent eyes, a beard, a goiter, a heart enlarged to the left, a blood pressure of 170 systolic and 104 diastolic, numerous striae cutis

distensae on the abdomen and thighs, hirsutism of the arms and legs and large brownish shiny pigmented areas over the thighs, chest and arms. The adiposity was largely confined to the trunk, the hands and feet being remarkably small relatively (fig. 1).

The Wassermann reaction was negative, the urine normal, the blood calcium 9.98 mg., the blood sugar 0.200 per cent and the nonprotein nitrogen 27.3 mg. The basal metabolic rate was plus 31 three months before entry and minus 1 in

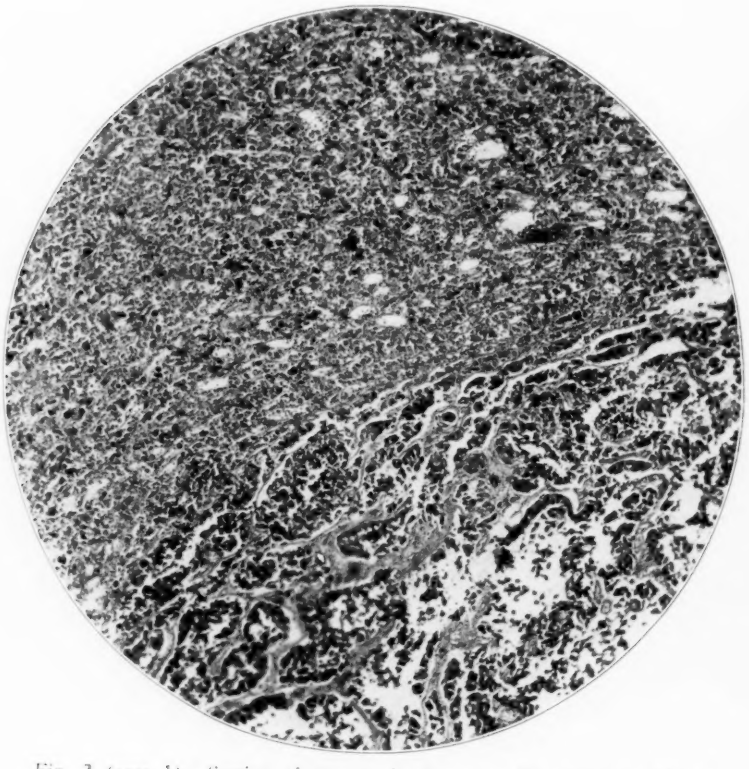

Fig. 2 (case 1).—Section of tumor, showing a rapidly growing basophilic papillomatous adenoma.

the hospital. Roentgen examination of the skull showed a normal sella turcica. Examination of the blood showed: hemoglobin, 106 per cent; red blood cells, 6,640,000, and volume of red cells per hundred cubic centimeters of blood, 53, a value distinctly above the normal for women.

The symptoms of goiter were so marked that it was felt that the adenomatous gland should be removed, the polyglandular disturbance being evident. On June 15, a subtotal thyroidectomy was performed, two enlarged hard lobes being removed. About seven days after the operation a psychosis developed with mild

convulsive seizures, the temperature rose to 100.2 F., and the patient died, sixteen days after operation, with symptoms of myocardial failure.

The postmortem examination was, unfortunately, limited to the head and the report was as follows: "Brain surfaces and meninges showed no exudate or hemorrhage. The pituitary body was symmetrically enlarged (1.75 by 1 cm.), and on cut section shows a small circumscribed area of whitish-gray tissue about 2 cm. in diameter (adenoma). Microscopically, there is a diffuse adenomatous

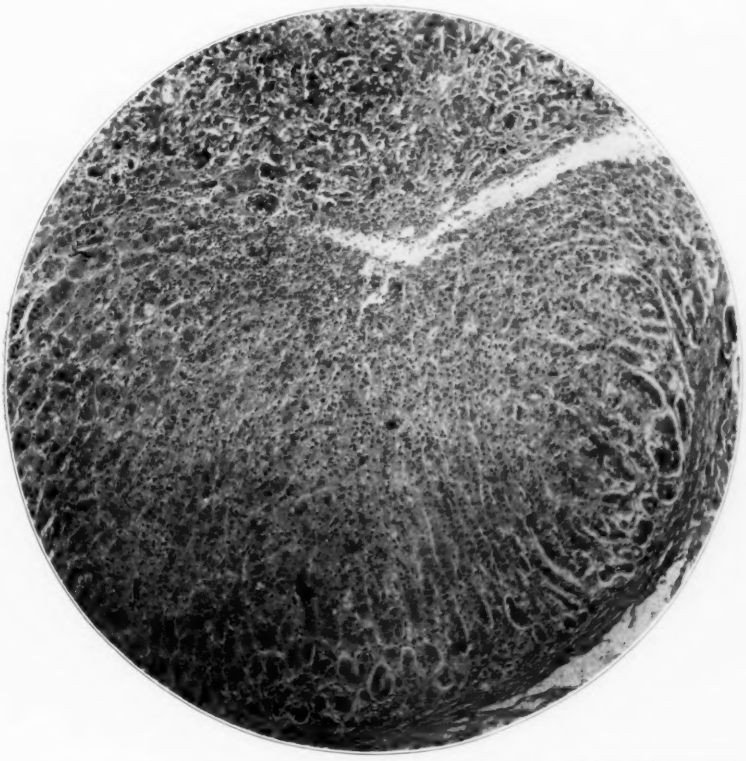

Fig. 3 (case 2).—Suprarenal cortex of uninvolved side, showing adenomatous hyperplasia.

hyperplasia of the pituitary body, including both the basophilic and eosinophilic elements. In one area of the anterior lobe there is a rapidly growing basophilic papillomatous neoplasm (fig. 2). The bone from the skull appears normal."

The following case represents an interesting association of a suprarenal tumor with hyperplasia of the hypophysis and a pronounced polycythemia.

Case 2.—Mr. S., a married, white laborer of 63 years, entered Harper Hospital in January, 1931, for repair of a left inguinal hernia and excision of a hydrocele on the same side (an industrial compensation case).

The past history and family history were entirely inconsequential. The patient's father, mother and siblings were all of average height and weight. He had never had any serious illness, and presented himself in perfect health. The hernia and hydrocele were repaired and the patient was sent home.

Fig. 4 (case 2).—Primary malignant neoplasm of the suprarenal cortex.

On February 15, he returned to the hospital complaining of vomiting and loss of weight. Examination disclosed a man in fair nutrition, not acutely ill. The only remarkable findings were a hard irregular mass, about 7 cm. in diameter, extending downward from the left costal margin and a smooth liver edge extending two finger breadths below the right costal margin.

Roentgen examination disclosed: ". . . evidence, we think, of pulmonary metastasis of a malignant neoplasm. Bilateral root deposit. Fluoroscopic evidence of enlarged liver and also questionably of the spleen. No indication of upper gastro-intestinal pathology. Cannot elicit definite evidence of malignancy in the lower bowel, although we could not exclude this condition."

The average values found in studies of the patient's blood may be summarized as follows: red blood cells, 8,194,000; hemoglobin, 153 per cent; reticulocytes, 1.3 per cent; polymorphonuclears, 95 per cent; lymphocytes, 5 per cent, and white blood cells, 8,000.

Over a period of fourteen days of observation no eosinophils or basophilic leukocytes were observed.

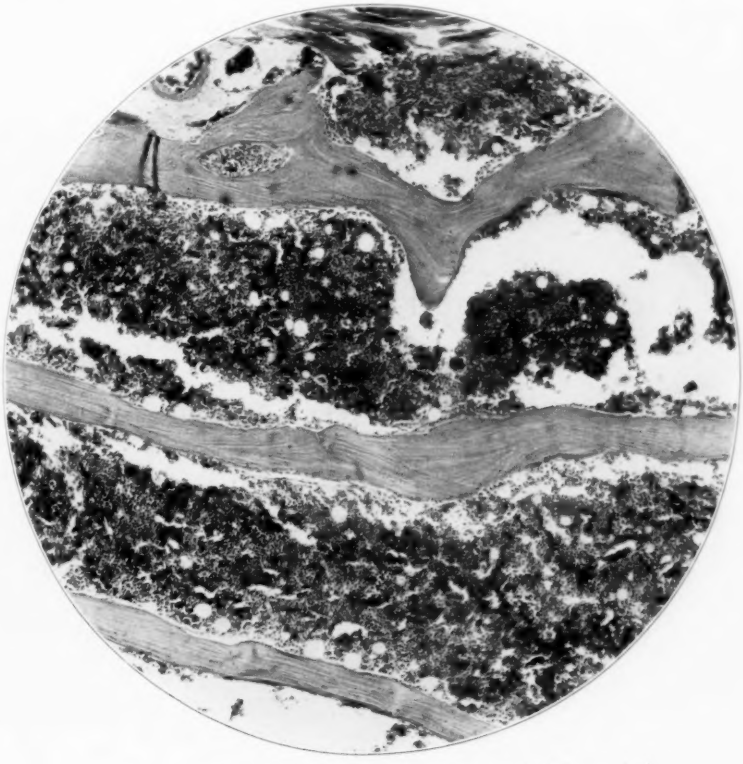

Fig. 5 (case 2).—Bone marrow, showing marked hyperplasia.

Urinalysis and tests of levulose tolerance gave negative results. The nonprotein nitrogen amounted to 30 mg.; the blood sugar to 0.095 per cent. The Wassermann test gave negative results; the test of liver function, results within normal limits.

At postmortem examination a large invasive tumor of the left kidney was found, which had metastatsized to the lungs. Microscopically, this tumor "is a malignant angio-mesothelioma with large pale staining cells. The structure is different from the ordinary type of Grawitz tumor, and in some areas is markedly reminiscent of decidual tissue. In other areas the structure resembles the ordinary type of polymorphonuclear cell sarcoma with many division figures and pseudo-giant cells." The pituitary was not remarkable grossly, but microscopically

showed "marked hypertrophy and hyperplasia of the basophilic elements." The bone marrow showed marked myeloid hyperplasia throughout the marrow space (figs. 3 to 6, inclusive).

Comment.—The first case was one of definite pituitary basophilism and duplicates those reported by Cushing.[1] The neoplastic type of basophilism is an interesting feature of the pituitary picture. The

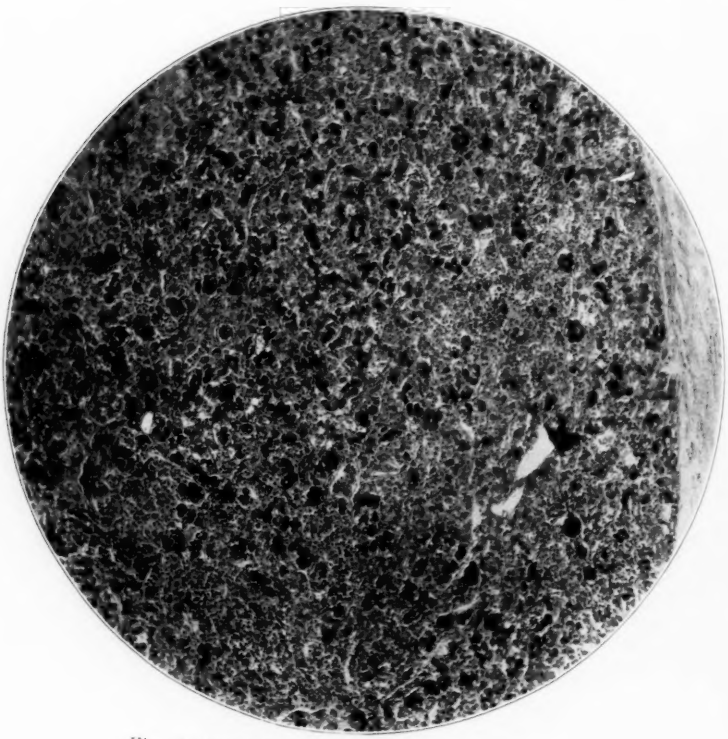

Fig. 6 (case 2).—Pituitary, showing basophilism.

polycythemia and spontaneous hemorrhages into the palms of the hands were striking features.

The second case shows that a primary involvement of the suprarenal cortex results in a secondary response on the part of the pituitary in the nature of basophilism. The polycythemia with a very high hemoglobin percentage was an outstanding feature.

EXPERIMENTS

In order to test the validity of the assumption that ablation of the suprarenal cortex induces compensatory physiologic overactivity of the

pituitary gland, as indicated by changes in its histologic structure and by the appearance of polycythemia, bilateral adrenalectomy was performed in eleven dogs and the blood picture observed. Only four dogs lived more than four days following operation, but in all cases an increase in the total number of circulating red cells was noted at the end of twenty-four hours; in the dogs that lived from four to six days this amounted to from 15 to 25 per cent, or an increase from the normal range of from 6,000,000 to 7,000,000 to over 8,000,000. In all save three the histologic picture of the pituitary gland changed within

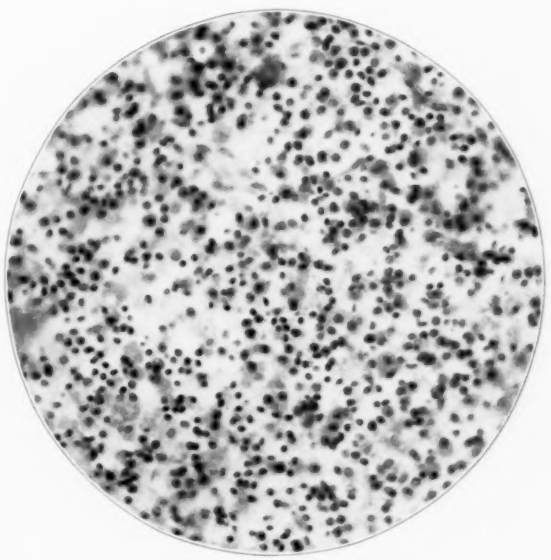

Fig. 7.—Pituitary of a dog (control).

twenty-four hours, to show a marked preponderance of basophils in contrast to the normal picture of almost complete eosinophilia. A series of ten pituitaries from normal dogs were studied to determine the normal histologic picture, which, as illustrated in figure 7, proved without exception to be a marked eosinophilia of the anterior lobe. In one case, however, an increase of 1,000,000 occurred in the red cell count and a marked eosinophilia was found in a microscopic study of the hypophysis, as shown in figure 8. In two other instances in which the period of survival was only twenty-four hours, no change in the normal eosinophilic picture was observed. The explanation of the eosinophilic picture in the former instance, in which a polycythemia was induced, is not clear. In every other instance a basophilic type of response was mani-

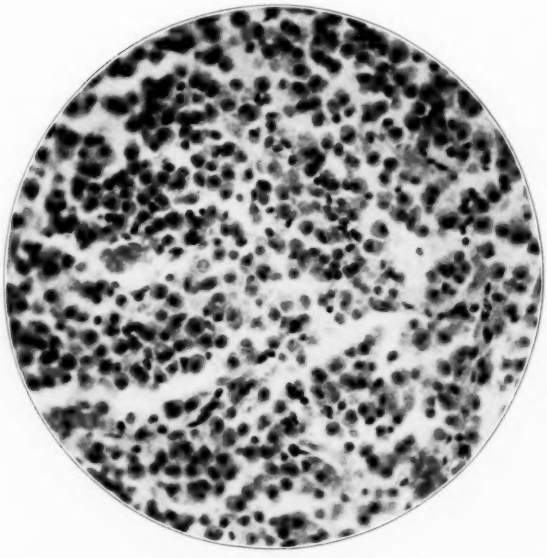

Fig. 8.—Pituitary of a dog, showing hyperplasia of the eosinophils.

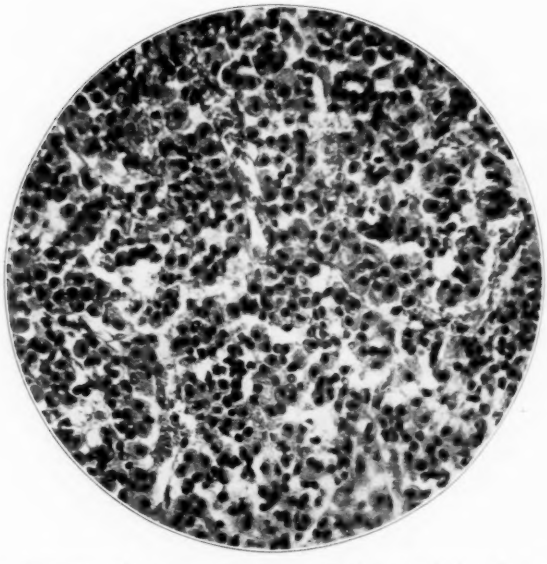

Fig. 9.—Pituitary of a dog, showing marked hyperplasia of the basophils twenty-four hours after adrenalectomy.

fested by the pituitary, even in one dog that lived only twenty-four hours; a histologic study of the pituitary in this animal is well illustrated by figure 9.

The reaction of one particular dog is noteworthy. A bilateral adrenalectomy was performed, and in forty-eight hours the red cell count had increased 15 per cent. Within four days the count had dropped to normal and the dog had completely recovered from the operation. An exploration was made, and a bean-sized remnant of adrenal gland was recovered, following which a polycythemia again

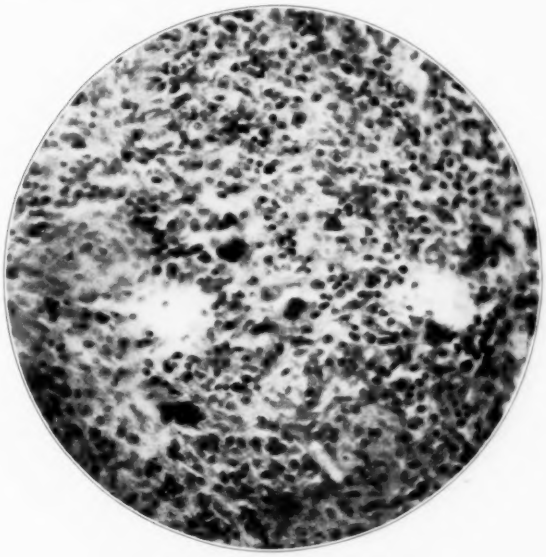

Fig. 10.—Myelosis of the spleen.

appeared. His pituitary showed a marked basophilia and also a myelosis of the spleen as illustrated in figure 10, a reaction noted in only three instances, however.

Thus, in acute adrenal insufficiency in dogs, there was a marked basophilic response in the pituitary with an associated polycythemia and a less constant myeloid change in the spleen.

From our studies we were impressed with the fact that both eosinophilic and basophilic adenomas have some features in common. For instance, hypertension is found in both conditions, and hyperglycemia, or a tendency to it, is also common to both. Hypertrichosis is a feature found in eosinophilism as well as basophilism. Polycythemia, as outlined in this paper, is likewise seen in both conditions, as is

kyphosis. This would seem to indicate that the unitarian cell theory of Collin,[78] postulating that the chromophobe cell is the mother of all pituitary cells, has certain facts to prove it. Be that as it may, the embryohormonic relation of the pituitary to the mesodermal tissues provides a logical explanation of the physiologic cell activity of this gland.

While the problem of tumor formation is somewhat aside from the present consideration, it is readily seen that the application of this embryohormonic principle to neoplasms is a logical sequence of thought. Certain clinico-pathologic observations strongly suggest that the pituitary-mesodermal relationship will prove to be of immense value in neoplasms of mesoblastic origin, particularly the sarcomas.

The experiments on dogs open up some debatable points which need not concern us here. It is realized that there are certain biologic differences between human beings and animals. Dogs do not sweat like humans, but use the respiratory mechanism instead. This may account for the increased number of red cells as compared with human beings. Adrenalectomy, with its effect on the respiratory system by increasing its load, produces a rapid increase in red cells. Experimental removal in animals does not, of course, duplicate the gradual *Organ Ausfall* of human beings, but polycythemia is seen often enough in atrophy of the suprarenal cortex in man to indicate some points of similarity. Then, too, the pathologic changes in the cells of the pituitary coming on so rapidly (in twenty-four hours) after extirpation of the adrenals lead one to believe that the chemical relationship between these glands (and, no doubt, between all endocrine glands) is a most intimate one.

SUMMARY

Two cases of polycythemia vera with pituitary basophilism, coming to autopsy, are described. One was a case of primary basophilic adenoma giving rise to the syndrome recently described by Cushing. The other was a secondary basophilism in response to a suprarenal tumor.

Experimentally induced polycythemia in dogs by bilateral adrenalectomy is also reported. In these animals rapid and marked hyperplastic changes of the pituitary cells were found. The hyperplasia was, in the majority of cases, confined to the basophil cells.

We endeavored to show:

1. The pituitary secretion has a very important influence on erythrocyte formation.

78. Collin, R.: La neurocrinie hypophysaire: Étude histophysiologique du complexe tubéro-infundibulo-pituitaire, Paris, G. Doin et Cie, 1928.

2. Primary disease of the suprarenal cortex results in secondary pituitary changes, thus accounting for many signs and symptoms erroneously ascribed to the suprarenal cortex.

3. The specific and selective embryohormonic relations of the pituitary gland to mesodermal tissues offer a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances.

INFECTIOUS POLYPOID COLITIS

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NASHVILLE, TENN.

The colon is a relatively frequent site for multiple polyps of the mucosa with and without chronic ulceration. The true polyp is composed of hyperplastic glandular mucous membrane projecting into the lumen of the bowel. In the literature are recorded cases of so-called pseudopolyposis lymphatica,[1] in which the mucosal projections are caused by underlying hyperplastic lymph follicles, but no cited instance has been found simulating the case to be reported, in which nodular polypoid projections into the colon were caused by a peculiar granulation tissue composed mostly of large mononuclear cells filled with what appears to be a specific infectious micro-organism.[2] It has not been possible to cultivate the bacillus associated with the lesion, but it is hoped that a record of the case may lead to an earlier recognition of the disease, so that its bacteriology may be studied with care.

REPORT OF A CASE

History and Course.—W. S., a 49 year old white truckman, entered the Vanderbilt University Hospital on Dec. 2, 1930, complaining of diarrhea. The onset was two months prior to admission with blood and pus in the stools, moderate tenesmus and constant but not severe griping pain in the left lower abdominal quadrant. The coexistence of fever could not be established. These symptoms continued, and the patient frequently had eight and nearly always six rather thin stools daily, until admission. Six weeks prior to admission anorexia and insomnia (not subsequent to pain) developed. One week before admission the patient had a severe chill, associated with nausea and vomiting. Following this he believed he had fever. He had had hemorrhoids, never acutely sore but inconstantly associated with fresh blood in his stools, over a period of five years preceding admission. He resided continually in Tennessee except for occasional short visits. His attack began while he was on a trip into Ohio.

On admission, the pulse rate was 100, the temperature, 99.8 F., and the respiratory rate, 22. The skin was loose and flabby, with marked loss of subcutaneous fat. Body lice were present. The palpable lymph nodes were not enlarged or tender. The lungs were clear. The heart was normal. A palpable, roughly defined, movable mass was present in the left lower abdominal quadrant. Numerous hemorrhoids were present. The extremities were normal. Reflexes were normal.

From the Department of Pathology, Vanderbilt University School of Medicine.

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2. Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, pt. 3, p. 847.

On the day following admission the patient had twenty-four bowel movements. He was given numerous sedatives to check the diarrhea, but with only moderate success.

The urine was essentially normal. The blood count showed: white blood cells, 5,500; red cells, 3,250,000; hemoglobin, 57 per cent; polymorphonuclears, 75 per cent, and polymorphonuclear basophils, 1.5 per cent. The Wassermann reaction was negative. The blood serum proteid showed: total, 5.4 mg.; albumin, 3.6 mg.; globulin, 1.85 mg., and albumin-globulin ratio, 2. The stools were frankly soft, bloody and purulent. Smears of stool showed a mixed flora and were negative for parasites. Proctoscopic examination showed multiple bleeding polypoid and ulcerated masses of the rectum. Roentgen examination with barium enemas showed marked narrowing of the rectum, with spasticity, constant but variable in degree. The region of the sigmoid showed fine irregularity, with nodular filling defects of the upper portion, suggesting polyps.

The patient remained in the hospital for four months and a half, with no real improvement. On March 8, 1931, exploratory laparotomy was performed. A large mass of perisigmoidal scar tissue was found about the sigmoid rectum. The incision was closed without further operation. Ten days after operation the incision broke open. No marked contamination occurred. The wound was reclosed. During treatment massive edema of the left leg developed, associated with a cylindric left popliteal mass. The patient died seventeen days after the laparotomy.

Postmortem Examination One Hour After Death.—The body was profoundly emaciated and multiple decubiti were present over the back and buttocks. A recent gaping surgical incision (laparotomy) was present, from which serosanguineous exudate was dripping. Smears from this wound showed gram-positive coccoidal bacteria. The superficial veins over Poupart's ligament on the left were markedly dilated. A definite cylindric mass was palpable in the left popliteal region and in the medial portion of the femoral triangle. The entire left leg was markedly edematous, and pitted on pressure.

The fatty tissue of the mesocolon, particularly the mesosigmoid, was coarsely trabeculated by dense bands of scar tissue which fixed the entire mesosigmoid and rectum rigidly to the abdominal wall in the region of the mesenteric attachment. The lymph nodes were small throughout the mesocolon and free from grossly recognizable tumor metastases. The heart was remarkable only for occasional scars and moderate brown atrophy. Multiple thrombi in the pulmonary arterial branches were associated with numerous acute infarctions of the lungs. There was thrombosis of the left popliteal, femoral and iliac veins. The liver and spleen were essentially normal, as were the kidneys, pancreas, suprarenals, stomach, duodenum, jejunum and ileum.

Beginning in the cecum and increasing in number and size as the sigmoid was approached were multiple sessile and pedunculated, rounded, gray, friable polyps. Associated with them were areas of ulceration. Some of the polyps were as much as 2 cm. long and 1 cm. in cross-section. Those of the colon above the sigmoid were for the most part covered by velvety epithelium. Those of the sigmoid and rectum, much the largest, were frequently ulcerated, their tips being necrotic and hemorrhagic. In no instance was there evidence of invasion of the submucous layers by epithelial tissue, although both the mucosa and the submucosa were frequently scarred and rich in granulation tissue beneath large ulcerated polyps. From such regions as these dense cicatricial bands frequently extended far into the extramuscular fatty tissue of the sigmoidal mesocolon and rectum. Sections for microscopic study were taken from all portions of the colon, including both polypoid and nonpolypoid areas.

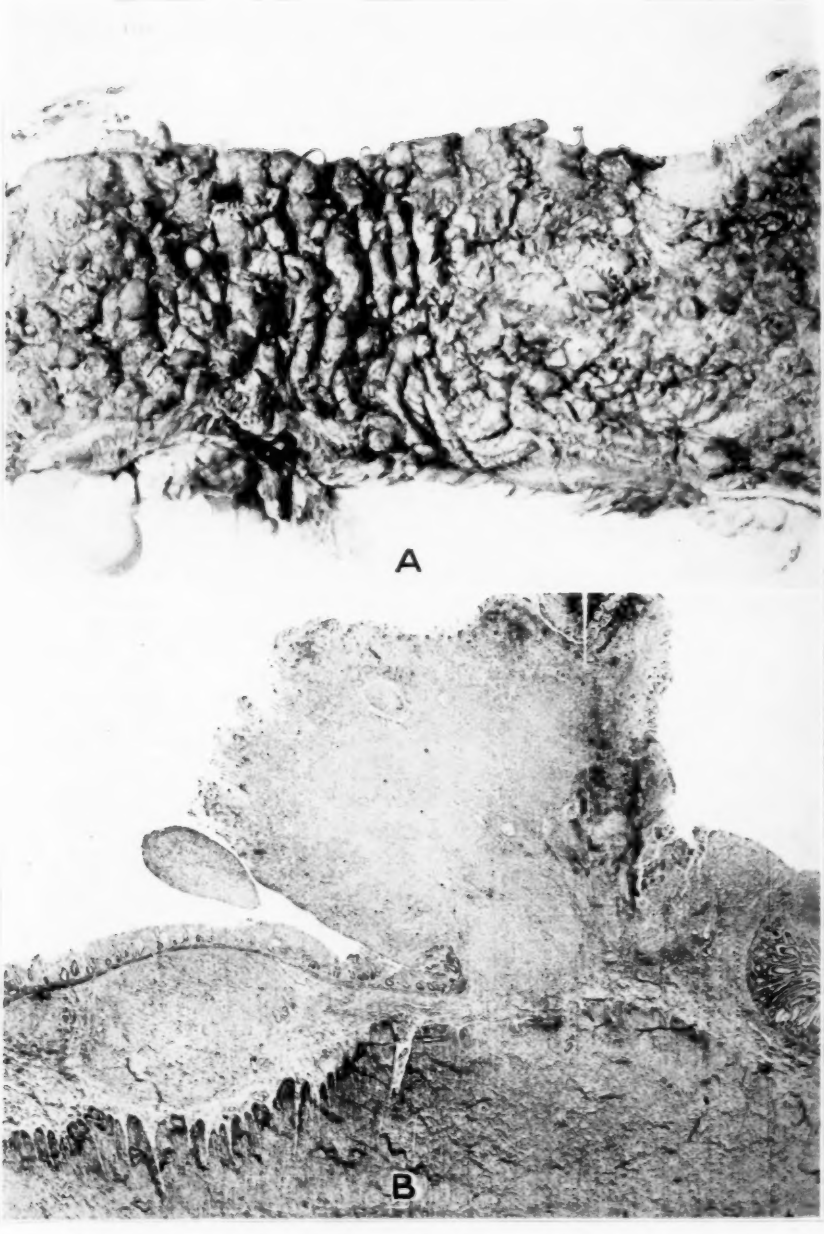

Fig. 1.—*A*, the colon, showing multiple pseudopolyps and ulceration. *B*, section under low magnification showing a pseudopolyp with surface ulceration. To the left is a submucous nodule of the specific granulation tissue that composes the larger pseudopolyp.

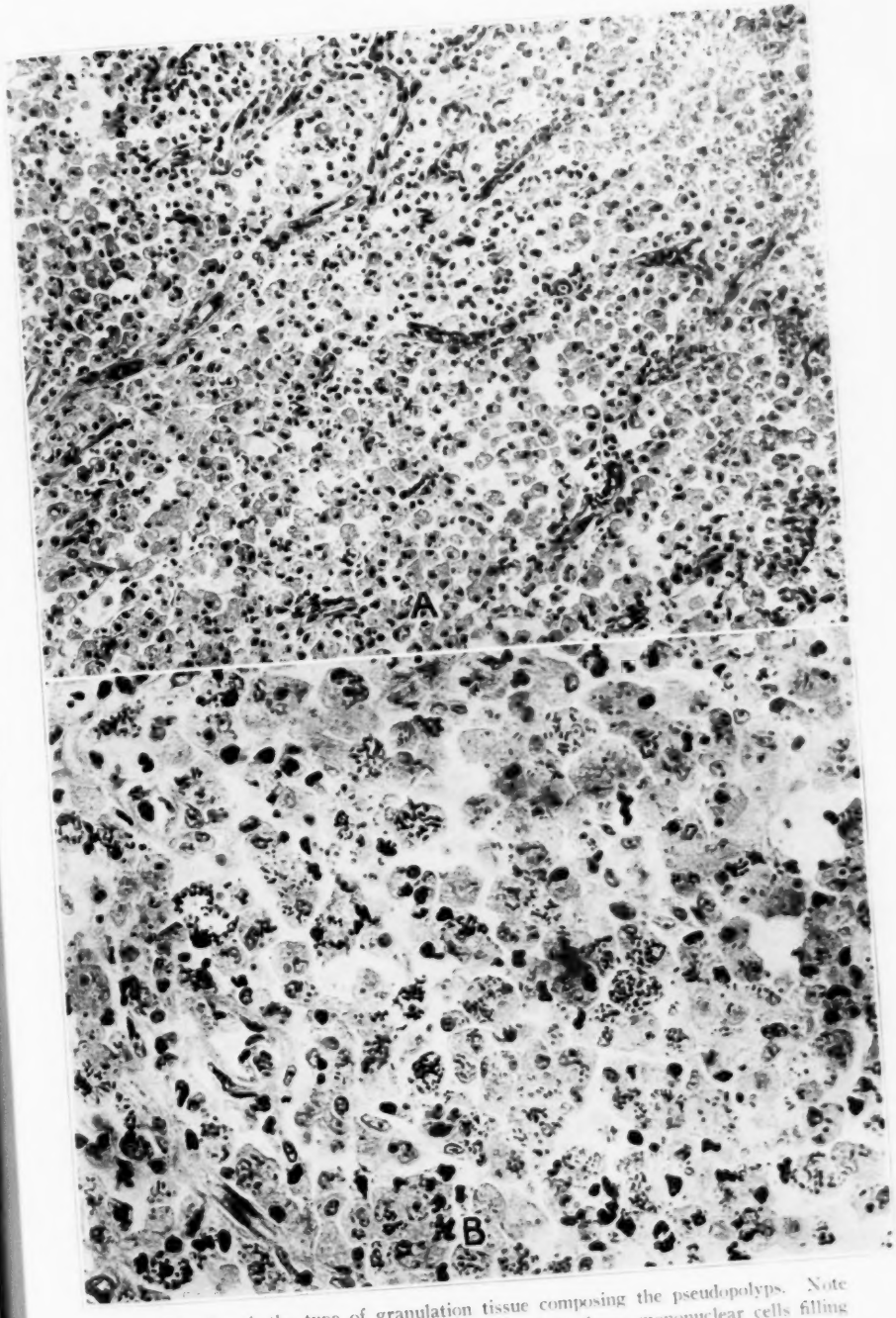

Fig. 2.—*A*, the type of granulation tissue composing the pseudopolyps. Note the delicate trabeculae carrying capillaries and the large mononuclear cells filling the interstices. *B*, distribution of micro-organisms in the inflammatory cells.

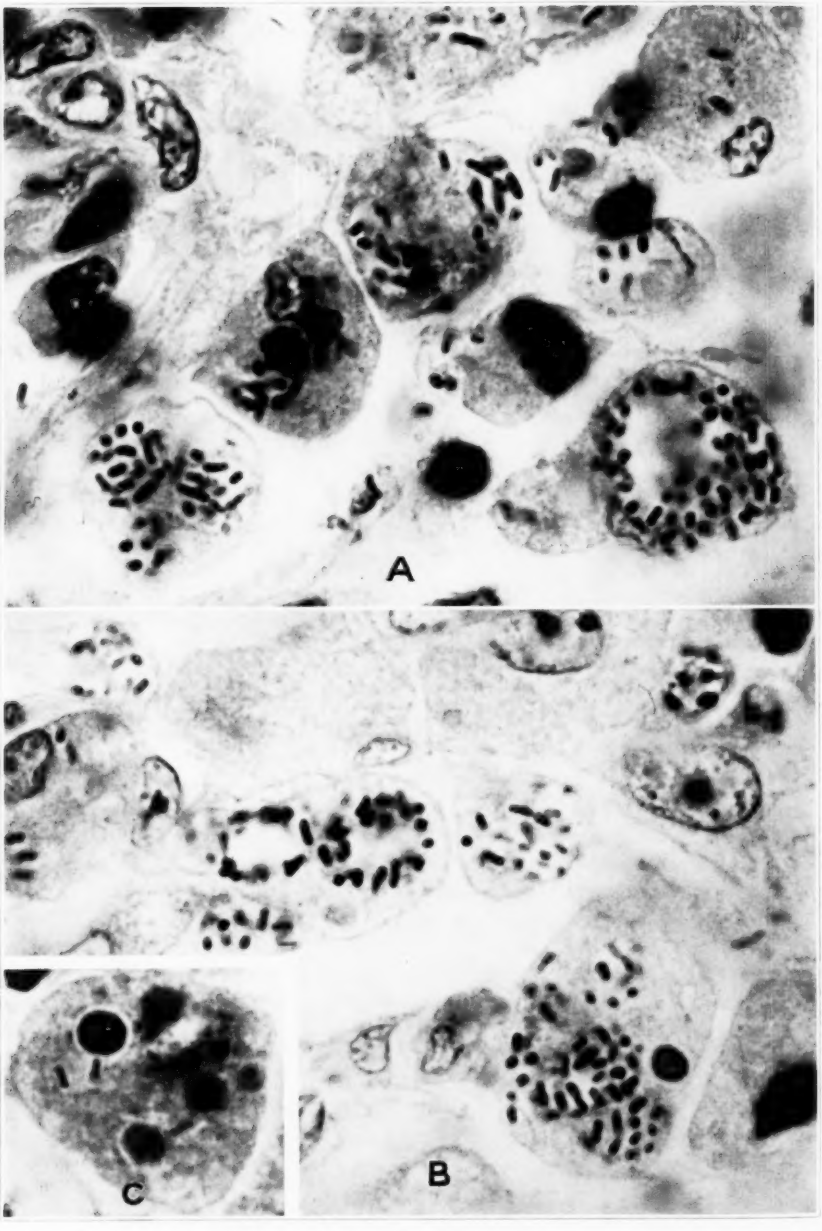

Fig. 3.—*A* and *B*, intracellular bacilli often arranged about spherical spaces (Goodpasture's stain). *C*, spherical intracellular inclusions.

On microscopic examination it was seen that the polypoid masses abruptly interrupted the surface contour of the colon. Often the mucosa was simply elevated to form a mound, but more frequently there were definite pedunculated polyps. The adjacent glandular structures, frequently hyperplastic, were prolonged, together with the muscularis mucosae, a short distance outward as a surface layer for the pedicle of the polyps. Beyond this both glands and connective tissue structures were obliterated by a massive aggregation of cells between which coursed only blood vessels and delicate fibrous tissue trabeculae. The surfaces of such polyps were frequently ragged and amorphous. The large mononuclear cells were situated in the submucosa and extended in a compact mass almost to the stratum muscularis, where they were limited by the outermost layers of the submucosal connective tissue. Similarly those masses of cells which simply elevated the mucosa without ulceration were distinctly circumscribed and confined to the submucosa and mucosal stroma, but were unencapsulated.

Cytologic study of the polypoid and circumscribed intramural cell clusters revealed a profound inflammatory reaction characterized primarily by cellular exudate. The inflammatory cells were practically all of the same kind. They were large mononuclear cells with abundant cytoplasm stained a pale pink and faintly granular in hematoxylin and eosin preparations, possessing dense, small nuclei. They bore a resemblance to the Mikulicz cells of rhinoscleroma, especially in that they contained numerous bacilli in their cytoplasm. They were free cells so closely packed throughout lymphatics and tissue spaces as to obliterate almost completely the normal architecture. No mitotic figures were seen. Frequently small focal areas of necrosis occurred in aggregations deep in the polypoid mass, and these areas were infiltrated with polymorphonuclear leukocytes. And, what is even more striking, the mononuclear cells were fairly uniformly stippled by numbers of small, pink-staining (hematoxylin and eosin) bacillary organisms often arranged in clusters within the cells, and frequently associated with large ovoid or circular, intensely pink, included bodies. Similar micro-organisms were found in numbers at the ulcerated surfaces where there was a polymorphonuclear exudate, but it appeared that the free bacteria might be derived in part at least from rupture and disintegration of the mononuclear cells in which they were confined elsewhere. Small lymph nodes adjacent to the involved colon showed moderate numbers of large mononuclears which contained the bacilli in intracytoplasmic groups.

The organisms, so abundant within the inflammatory cells, were rarely observed in an extracellular position, so seldom in fact that they appeared to have grown only inside the mononuclear cells. With the hematoxylin-eosin stain in tissue fixed in Zenker's fluid the bacteria were faintly pink; by Gram's method they did not retain the gentian violet and by the intensification, basic fuchsin staining of Goodpasture they took an intense purple-black stain. By the last method the intracellular bacteria were frequently found arranged about cystic spaces.

The included hyalin-like oval or spheroid bodies were stained red in the hematoxylin and eosin preparations and brownish purple by the carbolamilin-fuchsin stain. In almost all instances, if included structures were present, micro-organisms were also present, but in many cells micro-organisms were present without included structures. The inclusions bore no demonstrable relationship to the distribution of organisms within the cells.

Many gradations occurred in the state of inflammation of the different polyps studied. In some granulation predominated, but the specific inflammatory cells could always be found in relatively large numbers deep in such polyps.

Bacteriology.—Fresh tissues preserved at autopsy were, unfortunately, not cultured until they had been preserved in the icebox for three weeks because of a delay in the recognition of the nature of the lesion. At this time, after surface searing, deep cultures from polyps were taken and inoculated on Sabouraud's medium. Twenty-four hours later in all tubes characteristic ovoid, sticky, yellow-gray colonies developed in pure culture. This organism was isolated from six different polyps, but was never encapsulated and was constantly a gram-positive bacillus.

Animal Inoculation.—Subcutaneous injection of tissue into rabbits and guinea-pigs produced acute abscesses from which a gram-positive bacillus could be grown in pure culture on Sabouraud's medium. Inoculation with the organism transplanted from the polyps to Sabouraud's medium and grown in pure culture produced acute abscesses in rabbits, from which the organism could be recovered, but in which no intracellular organisms were demonstrable. Subcutaneous inoculation of monkeys (Macacus rhesus) produced transient acute inflammation which subsided spontaneously after three or four days.

COMMENT

So little is known of the origin of polyposis of the colon and the underlying factors associated with its existence that it seems advisable to present this case in which a specific micro-organism appears to have been responsible for a polypoid inflammation of the colon. The clinical symptoms simulated those of ordinary polyposis with ulceration, and occurred in association with structures which bore a close gross resemblance to ordinary polyps of the colon.

The extent of infection indicates that the organism described in these lesions was responsible for the colitis, and its widespread distribution suggests a high degree of pathogenicity, at least in susceptible subjects. This type of colitis has not, to my knowledge, been previously recognized either cytologically or bacteriologically.

The relationship of the organism to the individual cells is of interest. Their characteristic intracellular position can hardly be explained on the basis of phagocytosis and seems best interpreted by the supposition of an intracellular growth. The arrangement of the bacteria within the cell about the periphery of spherical spaces also indicates that the cellular cytoplasm is a suitable medium for their multiplication.

Unfortunately, nothing can be said of the origin of the inflammatory cells which are so strikingly typical of this inflammatory reaction. They have the appearance, however, of large mononuclear wandering cells. The origin of the inclusion-like structures within the cells is uncertain. Whether they are phagocytosed structures (which seems doubtful) or products of cellular degeneration has not been determined.

The bacteriologic studies in this particular case are valueless so far as actual demonstration of the etiologic agent is concerned. The organism isolated on Sabouraud's medium may well have been merely a con-

taminant, since in inoculation of animals intracellular organisms could not be satisfactorily demonstrated.

The case is reported in order to call attention to a hitherto undescribed polypoid colitis, due, it is believed, to a specific gram-negative, apparently unencapsulated bacillus. The characteristic lesion is a specific inflammatory tissue composed almost entirely of large mononuclear cells which contain within them the etiologic agent.

SUMMARY

1. A case of ulcerative polypoid colitis, with a typical clinical history of an infectious ulcerative colitis and the roentgenologic findings of polyposis, with suspected malignancy, is reported. This type of lesion in the colon has apparently not been described before.

2. The polyps are composed primarily of accumulations and massive clusters of large mononuclear inflammatory cells which contain the infectious agent.

3. The etiologic agent is a gram-negative bacillary organism situated for the most part within large mononuclear leukocytes. The microorganism has not been cultivated, nor were distinctive lesions induced in animals by inoculation with infected tissue.

TUBERCULOSIS OF THE MYOCARDIUM

REPORT OF SIX CASES, WITH OBSERVATIONS ON INVOLVEMENT OF CORONARY ARTERIES

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While tuberculous pericarditis is not uncommon, tuberculous involvement of the myocardium is decidedly rare. Some idea of the incidence of the latter condition can be gained from the reports of Raviart [1] and Norris,[2] the former finding only 49 cases among 7,683 autopsy reports collected from French and German sources, and the latter 5 cases among 7,319 protocols. In all, we have been able to find reports of only a few more than 200 instances of tuberculous myocarditis (Raviart,[1] Norris [2] and others [3]).

From the Divisions of Cardiology and Pathology of the Philadelphia General Hospital and the Robinette Foundation of the University of Pennsylvania.

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2. Norris, G. W.: Tuberculous Pericarditis Based on a Study of 7,219 Autopsies in Philadelphia Hospitals, Univ. Pennsylvania M. Bull. **17**:155, 1904.

3. (*a*) Adamson, W. W.: A Case of Tuberculosis of the Myocardium, J. Path. & Bact. **23**:399, 1920. (*b*) Anders, J. M.: Tuberculosis of the Myocardium, J. A. M. A. **39**:1081 (Nov. 1) 1902. (*c*) Beifeld, A. F.: Tuberculosis of the Myocardium with Report of a Case, Tr. Chicago Path. Soc. **8**:104, 1909-1912. (*d*) Benda, C.: New Cases of Tuberculosis of the Myocardium with Report of a Case, Tr. Chicago Path. Soc. **8**:104, 1909-1912. (*e*) Berger, L., and Miller, J. C.: Solitary Tuberculosis, Virchows Arch. f. path. Anat. **273**:250, 1929. (*f*) Bettoni, L.: Cases of Tuberculous Myocarditis with Multiple Nodes, Cuore e circolaz. **13**: 210 and 223 (May) 1929. (*g*) Binder, H.: Tumor-Like Tuberculosis of the Heart, Zentralbl. f. inn. Med. **41**:462, 1920. (*h*) Brockhausen, K.: Unusual Case of Tuberculous Myocarditis, Virchows Arch. f. path. Anat. **318**:274, 1929. (*i*) Carson, W. J.: Disseminated Tuberculosis; Caseous Tuberculosis of Thymus and Myocardium, M. J. & Rec. **119**:281, 1924. (*j*) Demme: Beiträge zur Tuberculose des Kindesalters und ein Fall von primärer Tuberculose des Herzmuskels, Wien. med. Bl. **10**:1545, 1887. (*k*) Dillon, E. S.: Tuberculous Pericarditis with Tuberculosis of Myocardium and Endocardium, M. Clin. North America **10**:253 (July) 1926. (*l*) Doerner: A Case of Conglomerate Tuberculosis of the Heart, Diss. Jena, 1918. (*m*) Ellis, A.: A Heart Showing Chronic Tuberculosis of the Pericardium with Involvement of the Myocardium, Proc. Path. Soc., Philadelphia **6**:198, 1902. (*n*) Gallavardin, L., and Gravier, L.: Tuberculous Interstitial

In spite of its apparent rarity, we have secured during the past year six examples of tuberculous myocardial involvement from the postmortem material of the Philadelphia General Hospital. A brief history of these cases follows.

REPORT OF CASES

CASE 1.—*History.*—F. E., a colored woman, aged 51, was admitted to the neuropsychiatric wards of the Philadelphia General Hospital on Oct. 7, 1930, because of dizziness and attacks of unconsciousness of from five to twenty minutes' duration, which first appeared five months before admission. The attacks, probably the result of syphilis of the nervous system, which undoubtedly was present, obscured to a large extent the cardiac symptoms. Evidence of slight congestive cardiac failure in the form of breathlessness and edema were, however, revealed by the history. The family history was irrelevant.

Examination.—Initial examination revealed a somewhat undernourished middle-aged woman who did not appear acutely ill. Nothing abnormal was found in the examination of the head, neck, lungs, abdomen and extremities. The heart was found to be slightly enlarged and its rate rapid, but otherwise not noteworthy. The blood pressure was 124 systolic and 80 diastolic; the radial arteries showed moderate thickening.

The Wassermann tests of the blood and spinal fluid were strongly positive, and a dementia paralytic colloidal gold curve was present. Other laboratory studies revealed nothing of note. Neither roentgen nor electrocardiographic examination was obtained.

Course.—During the six months' observation the attacks of unconsciousness became more frequent and finally were accompanied by convulsive phenomena. The patient had a continuously elevated temperature (from 99 to 101 F.); her pulse and respiration rates steadily increased until they were 140 and 40, respectively, just before her death. Preceding death, her lungs, previously normal, began to show basal râles, which led to a diagnosis of bronchopneumonia, the final diagnosis being dementia paralytica and bronchopneumonia.

Necropsy.—The pericardium was thickened and adherent to the heart and adjacent mediastinal structures, and to the left lung. The heart and attached pericardium weighed 300 Gm. Where the pericardial adhesions could be freed, the epicardial surface was seen to be thickened and white or grayish red. Bulging from the anterior wall of the right auricle and from its appendage was a yellowish-white, irregularly smooth, firm mass, measuring 3 cm. in length, 2.25 cm. in

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Myocarditis, Arch. d. mal. du coeur **21**:472 (July) 1928. (*o*) Gunnewardene, T. H., and Gunnewardene, H. O.: Extensive Primary Tuberculous Disease of the Heart, Proc. Roy. Soc. Med. **13**:38, 1919-1920. (*p*) Oudendal, A. J. F.: Spontaneous Rupture in Tuberculous Myocarditis, Nederl. tijdschr. v. geneesk. **1**:2087 (May 19) 1921. (*q*) Passamonti, M.: A Case of Tuberculosis of the Myocardium, Policlinico (sez. prat.) **14**:88, 1907. (*r*) Perreti, V. R.: Concerning Diffuse Nodular Tuberculosis of the Myocardium, Pathologica **21**:566, 1929. (*s*) Pic, A., and Morénos, L.: Tuberculose cardio-vasculaire, Paris, Gaston Doin, 1930. (*t*) Thomson, J. G.: An Unusual Case of Diffuse Tuberculous Infiltration of the Myocardium, J. Path. & Bact. **33**:259, 1930. (*u*) Toldt, G.: A Case of Tuberculosis of the Myocardium, Rev. de méd., Paris **26**:101, 1906. (*v*) Weiss, E.: Tuberculosis of the Heart, Arch. Int. Med. **29**:64 (Jan.) 1922.

width and 1 cm. in depth, which on section was seen to bulge into the lumen of the right auricle and into the adjacent appendage and to have destroyed and replaced the muscle of the auricular wall, which it had invaded (fig. 1). The endocardium underlying the mass and the adjacent auricular muscle were studded with fairly large tubercles, in which rough, pinpoint ulcerations could be seen.

The myocardium of the rest of the heart was pale and exceedingly soft, but presented no other gross evidence of tuberculosis. The valves were normal, and the coronary vessels were smooth and patulous on gross examination.

The bronchial and mediastinal glands were enormously enlarged; on section they were yellowish white but of fairly firm consistency, and showed no caseation.

Fig. 1 (case 1).—Large caseous tumor, *C.T.*, in the wall of the right auricle.

Both lungs were infiltrated throughout by pinpoint miliary nodules, which were notably uniform in size and were less numerous toward the periphery than in the center of the lungs. The pleural surfaces were thickened much in the same manner as the pericardium.

All the other viscera were infiltrated by miliary tubercles, the uniform distribution and size of which indicated that rapid, overwhelming bacillemia had taken place.

Histopathology of the Heart.—One section taken from the right auricular wall consisted mainly of a large, caseous nodule that had almost entirely replaced the muscle and was surrounded by narrow zones of epithelioid and large round cells. The remaining muscle showed marked swelling and vacuolization of fibers and considerable infiltration by large endothelial cells, the latter being practically the

only type of cell called forth. The arteries present were small (arterioles) and frequently showed localized thickenings of the intima without cellular infiltration.

A second section obtained from the left ventricle showed a subacute plastic pericarditis, the epicardium having been invaded by collections of endothelial cells, fibrin and young connective tissue permeated by newly formed blood vessels. An interstitial myocarditis was also present in the form of small and large collections of endothelial cells, accompanied by a gelatinous edema. Submiliary foci of epithelioid cells were also present around small blood vessels. The muscle, in spite of the interstitial reaction, was rather well preserved in many parts, to judge by the staining, striation and nuclear appearance. In this second section, obtained at a distance from the caseous mass in the auricle, small arteries occasionally showed a pear-shaped or drop-shaped acellular bulging of the intima. The larger vessels were uninvolved. The capillaries showed endothelial hyperplasia.

The complete pathologic diagnosis was tuberculous pericarditis, nodular caseous tuberculosis of the right auricular muscle, diffuse interstitial tuberculous myocarditis, tuberculous arteriolitis, generalized miliary tuberculosis of the lungs and other viscera, and tuberculous mediastinal lymphadenitis.

CASE 2.—*History.*—H. H., a white man, aged 72, was admitted to the psychopathic wards of the Philadelphia General Hospital on Dec. 11, 1930. He was quite incoherent, and for this reason the only facts discovered were that he had suffered from a painful spine for seven months, and that he had become progressively weaker.

Examination.—Initial examination revealed an asthenic, slightly cyanosed old man, who, though very weak, was apparently not in great distress. Nothing of importance was found in the examination of the head, neck or abdomen. Retraction of the supraclavicular fossa, slight impairment, bronchovesicular breath sounds unaccompanied by râles and increased vocal fremitus at the apex of the right lung led to a clinical diagnosis of old, healed apical tuberculosis. The heart was slightly enlarged in the transverse diameter, and at the apex were heard a soft systolic murmur and heart sounds that were thought to be definitely impaired in intensity. An irregular rhythm led to a clinical diagnosis of auricular fibrillation, but no electrocardiogram was obtained to confirm this diagnosis. The blood pressure was 130 systolic and 90 diastolic, and the peripheral arteries were markedly sclerosed. The spine was painful on motion and on fist percussion over the lumbar vertebrae. The only laboratory examinations obtained before death were urinalysis, which gave negative results, and a roentgen examination of the spine, which confirmed a clinical diagnosis of spondylitis of all the lumbar vertebrae. It was noted, however, that the body of the third lumbar vertebra was narrowed.

Course.—Asthenia became progressively more marked and led to death five days after admission. During this period of observation, the temperature ranged between 96 and 99 F., the pulse rate between 110 and 130, and the respirations between 22 and 32.

The clinical diagnosis was generalized arteriosclerosis, myocardial degeneration with auricular fibrillation, healed pulmonary tuberculosis and lumbar spondylitis.

Necropsy.—The heart, pericardial sac and mediastinal lymph nodes, which were removed en masse, weighed 1,000 Gm. The loosely adherent, thickened parietal pericardium, measuring as much as 6 or 7 mm. when pulled away from the visceral layer, revealed a characteristic "bread and butter" fibrinous surface. Its cut surface had a grayish, translucent appearance and was quite tough at times, being of almost cartilaginous consistency. The epicardium was thickened over all chambers, particularly the right auricle. The outer yellowish-white, shaggy portion was clearly separated from the myocardium by a zone of grayish, translucent tissue,

except over the roof of the right auricle, where it definitely invaded and destroyed the myocardium (fig. 2). No definite caseation was found.

Including the epicardium, the left ventricle at its midportion measured 22 mm. in thickness; the right, 12 mm.; the right auricle in its anterosuperior aspect, 8 mm., and the left, 6 mm. The myocardium was a normal reddish brown and was moderately firm. The valves, the root of the aorta and the orifices of the coronary arteries showed nothing of importance, while the larger coronary branches, although they showed considerable calcareous infiltration, were patulous wherever dissection permitted inspection.

The mediastinal lymph nodes showed early and moderate caseous degeneration, while the bronchial nodes were large and calcified. The pleura was neither thickened nor adherent, and no free fluid was present. The lungs showed nothing of

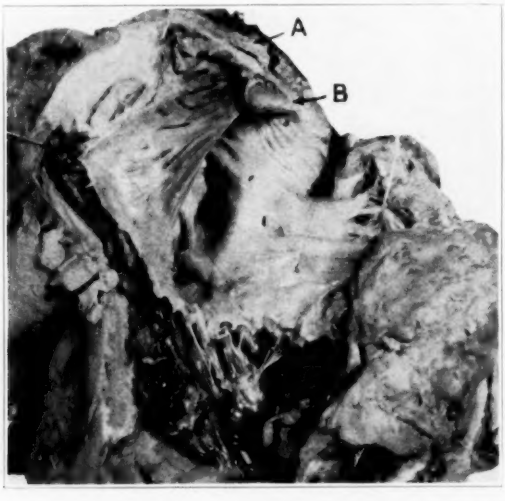

Fig. 2 (case 2).—*A*, tuberculous pericarditis, and *B*, secondary invasion of the right auricle.

note, except healed apical tuberculosis about the size of a ten-cent piece in the upper right lobe.

The lower portion of the second, the greater portion of the third and the intervertebral disk between these lumbar vertebrae showed typical tuberculous necrosis. Beneath the iliopsoas muscle of each side was a well localized collection of tuberculous pus. The pathologic findings in other viscera are indicated in the pathologic summary.

Histopathology of the Heart.—The sections studied were taken from the anterior and superior wall of the right auricle. The outer portion of the thick pericardial layer consisted of caseation, while the inner portion showed an active, proliferative, inflammatory process, with many tubercles, giant cells and diffuse fibrosis, which invaded the epicardial fat and auricular muscle. The mild form of involvement of the muscle consisted of distention of the fibers by a gelatinous edema, with sparse infiltration of fibroblasts and occasional endothelial cells. In this type of involvement the individual fibers stained fairly well, and the nuclei

were apparently undamaged. In other instances the infiltration was more intense and destructive; large and small nodules of endothelial and round cells were found to extend through the muscle and reach the endocardial surface. Accompanying this nodular infiltration was local destruction of muscle. In the two larger arteries, as well as the smaller vessels, a moderate acellular, intimal proliferation was present, though no definite thrombosis was observed. Tubercle bacilli, while not numerous, were found in specially stained sections of the myocardium.

The complete pathologic diagnosis was summarized as follows: chronic adhesive, tuberculous pericarditis, with secondary tuberculous infiltration of the right auricle; tuberculous arteritis; healed apical tuberculosis of the right lung; caseous tuberculosis of the mediastinal nodes and calcification of the peribronchial lymph nodes; tuberculosis of the second and third lumbar vertebrae, with early abscess of the psoas muscles; coronary sclerosis; moderate myocardial fibrosis; hypertrophy of the left, and dilatation of the right, ventricle; moderate arteriosclerosis of the aorta; acute toxic splenitis; chronic passive congestion of the liver, and nephrosclerosis.

CASE 3.[4]—*History.*—D. S., a Russian laborer, aged 46, was admitted to the medical wards of the Philadelphia General Hospital on Feb. 23, 1931, because of persistent cough, pain in the right side of the chest and progressive weakness of two months' duration. His family history was unimportant.

Examination.—The essential findings were confined to the lungs and heart. The former showed definite evidence of fibrocaseous tuberculosis, involving both lungs (confirmed by a roentgenogram); the heart showed marked enlargement in the transverse diameter; the heart sounds were distant and feeble, but no murmurs were audible. There were a rapid, regular rhythm and pulsus paradoxus, with a blood pressure of 100 systolic and 60 diastolic. Fluoroscopic examination revealed considerable enlargement of the cardiac silhouette with little systolic excursion of the ventricles. A diagnosis of pericardial effusion was confirmed by pericardial tap. Further laboratory findings revealed a low white blood count and tubercle bacilli in the sputum and pericardial fluid.

Course.—The patient was treated by repeated pericardial tappings with reinjections of air, a total of 20 such procedures being performed. As much as 1,200 cc. of fluid was removed at a time. The amounts of fluid withdrawn became smaller and smaller, and eventually there occurred a plastic obliteration of the sac. The exudate was usually serous, although occasionally turbid. Tubercle bacilli were recovered twice.

The temperature ranged from 99 to 104 F., with daily elevations; the respirations ranged from 20 to 30, and the pulse rate, from 93 to 145 per minute. The electrocardiogram on Feb. 18, 1931, showed extremely low amplitude of the ventricular complexes in all leads, with inversion of the T waves in leads I and II. For two months the patient did well, showing a surprising lack of symptoms. About May 1, 1931, however, numerous auricular extrasystoles were noted and remained in evidence. From this point on the patient grew progressively weaker, and death occurred rather unexpectedly on June 1, 1931.

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4. Several months before death, Dr. Thomas Klein (Treatment of Tuberculous Pericarditis with Effusion by Artificial Pneumopericardium, Tr. Am. Climat. & Clin. A. **47**:61, 1931) reported this case from the point of view of the benefit of frequent tapping and the production of pneumopericardium in preventing the reaccumulation of fluid. At the time of his report, as will be pointed out, it is probable that the myocardium had not yet become involved.

The clinical diagnosis was fibrocaseous tuberculosis of both lungs and tuberculous pericarditis, with probable tuberculous myocarditis.

Necropsy.—The parietal and visceral layers of the pericardium were uniformly thickened by fibrocaseous tuberculosis. In many places the layers were loosely adherent, and the sac obliterated, while in others loculations contained small amounts of thick, greenish-yellow fluid. The heart proper was apparently slightly decreased in size, although its walls, including the epicardium, were markedly thickened. The left ventricle measured 25 mm. in thickness at its midportion, the pericardial caseation contributing 10 mm. of this thickness; the right ventricle, 10 mm., half of which was formed by pericardial exudate. Tuberculous involvement of the myocardium was found in a small portion of the right auricle lateral to the orifice of the superior vena cava. The muscle at this site was pale and gelatinous in appearance, and the overlying pericardium could not be dissected away.

The tuberculous involvement of other organs is indicated in the pathologic summary.

Histopathology of the Right Auricle.—The epicardium was greatly thickened by caseation and tuberculous granulation tissue. The latter showed its greatest cellularity at the border of the myocardium, into which there was occasional patchy infiltration of groups of large endothelial cells, the cytoplasm of which was often acidophilic. These focal collections were small, scattered and not accompanied by caseation, and contained an occasional giant cell. The muscle fibers were moderately swollen and in some areas disintegrated. The focal necrotic areas contained large endothelial cells and lymphocytes. There was also observed widespread interstitial edema, which in places had a gelatinous appearance. The endocardium was not involved except at one point, where a focal cellular collection had developed, which extended almost to the endocardial surface; however, no ulceration or thrombosis had developed. Large blood vessels were not seen in these sections, but small vessels, particularly arterioles, showed a remarkable endothelial hyperplasia. Occasional perivascular collections of round cells were also noted.

The complete pathologic diagnosis was tuberculous pericarditis, with secondary infiltration of the right auricular muscle; tuberculous arteriolitis; widespread fibrocaseous tuberculosis of both lungs, complicated by tuberculous bronchopneumonia of the left lower lobe; terminal miliary tuberculous invasion of the spleen, kidneys and liver, and caseous, tuberculous, mediastinal lymphadenitis.

CASE 4.—*History.*—E. H., a colored woman, aged 26, was admitted to the wards for patients with tuberculosis of the Philadelphia General Hospital, on May 6, 1931, because of a productive cough, progressive loss of weight and a chronic, discharging lesion of the left foot. Her symptoms began in May, 1930, following an attack of pleurisy, and had since been progressive. In July, a slight trauma to the left ankle led to the development of an abscess, which did not heal after incision. The patient's past and family history revealed nothing of note.

Examination.—The essential findings revealed by examination were evidence of tuberculous infiltration diffusely disseminated throughout both lungs, with cavitation at the apex of the right lung. The heart was moderately enlarged in the transverse diameter; no murmurs were audible. The blood pressure was 95 systolic and 60 diastolic. There was a large chronic ulcer on the dorsum of the foot, from which there was considerable drainage with a foul odor.

Course.—The temperature ranged from 99 to 103 F. and the pulse rate, from 100 to 130. The results of the laboratory studies were not of importance, except that the roentgen examination revealed transverse enlargement of the heart and disappearance of the normal contour of the left border, in addition to acute pul-

monary tuberculosis. Progressive asthenia culminated in death, on May 26, 1931. The clinical diagnosis was bilateral, chronic ulcerative tuberculosis, tuberculous osteomyelitis of the left ankle and tuberculous pericarditis with effusion.

Necropsy of the Heart.—The heart and its thickened pericardial sac weighed 600 Gm. The parietal and visceral pericardium was the seat of an advanced caseous tuberculosis and was so adherent that these layers could be separated only with difficulty. The myocardium was pale and exceedingly soft. Except for the overlying thickened adherent pericardial layers, which measured from 1 to 3 cm., the ventricular walls were not enlarged. There was no definite myocardial infiltration, except in the roof of the right auricle, where the muscle over a small area had a yellowish-gray, almost gelatinous, appearance. At this point its demarcation from the thickened pericardium was obscured. No gross caseation was seen, nor were any points of endocardial ulceration present. There was no pathologic complication of the veins, and the lumens of the coronary arteries were grossly normal. (The important pathologic findings in other organs are indicated in the summary of the pathologic examination.)

Histopathology of the Heart.—Section of the right auricle showed the epicardium to be tremendously thickened by fibrocaseous tuberculosis. The thickened pericardium could be roughly divided into an outer layer of caseation and an inner cellular layer with dense infiltration of endothelial and round cells, accompanied by numerous giant cells. In some fields the myocardium showed marked focal parenchymatous degeneration, the striations having disappeared and the fibers having disintegrated; a poorly stained seminecrotic mass of fibrils remained, into which a sparse collection of epithelioid cells had infiltrated. In other fields there were focal collections of large endothelial cells, many of which had eccentric nuclei and more or less acidophilic cytoplasm. In one such focus there was a large giant cell, but caseation was not present. The small capillaries showed marked endothelial hyperplasia.

A second section through the right ventricular wall also showed a thick, cellular, tuberculous infiltration of the epicardium, most dense immediately outside the myocardium. Occasionally small clusters of large endothelial cells were seen within the myocardium, usually around the lymphatics or near small blood vessels.

A third section taken through the ventricular septum included the anterior descending artery. The latter was adjacent to a large tuberculous lesion in the epicardium, but its adventitia was not infiltrated by it. It showed, however, a marked proliferation of the intima, which was almost uniformly involved, the thickening being produced, not by cellular infiltration, but apparently by swelling and vacuolization of the intima. The elastic laminae were intact, and the media was normal throughout. The changes due to ordinary arteriosclerosis were not present.

The complete pathologic diagnosis was tuberculous pericarditis, with secondary infiltration into the right auricle; tuberculous arteritis of the anterior descending coronary artery; generalized caseous, nodular tuberculosis of both lungs, with multiple secondary abscesses; caseous mediastinal glandular tuberculosis, and miliary tuberculous infiltration of the spleen.

Case 5.—*History.*—C. J., a colored boy, aged 16, entered the medical wards of the Philadelphia General Hospital on May 11, 1930, because of precordial pain, breathlessness and cough. Indefinite pain in the upper right side of the abdomen was first noticed three months before admission and was soon followed by dyspnea. The pain soon changed its site to the precordium, and there became permanent and extremely severe. Cough was present but not striking, and had never been accompanied by hemoptysis. Neither the past nor the family history was important.

Examination.—On initial examination, the patient was found to be toxic, restless and harassed by severe precordial pain. No evidence of significant abnormalities were found in the head, neck, lungs, abdomen and extremities. Two important cardiac findings—great enlargement and muffled sounds—led to a diagnosis of pericardial effusion. After two unsuccessful pericardial taps, the diagnosis was changed to adhesive tuberculous pericarditis.

Course.—During the first three months of observation, the patient improved slightly. Thereafter his course was gradually but steadily downward. In view of the increase in the size of the cardiac silhouette, a third pericardial paracentesis was performed, on Sept. 28, 1930, and yielded 8 cc. of thick, greenish, necrotic material, which contained many tubercle bacilli. This proved the clinical diagnosis. Evidences of cardiac failure became more and more marked, pulmonary congestion

Fig. 3 (case 5).—Roentgenogram taken on Nov. 15, 1930. The diagnosis was tuberculous pericarditis.

and edema progressively increasing, the pulse rate rising, and auricular fibrillation finally developing shortly before death, on Nov. 4, 1930.

During eight months' observation the temperature ranged between 99 and 101 F. Many leukocyte counts ranged between 6,000 and 11,000, with normal differential counts. The Wassermann reaction, the chemical examination of the blood and blood cultures gave negative results, and repeated examinations of the sputum failed to reveal tuberculosis bacilli. All roentgen examinations (fig. 3) showed the lungs to be uninvolved by tuberculosis and revealed a large cardiac silhouette that could not be differentiated from pericardial effusion. The electrocardiogram, as early as April 10, 1930, showed definitely inverted T waves in leads I and II, and by Oct. 2, 1930, auricular fibrillation and ventricular complexes of extremely low amplitude followed by inverted T waves. The clinical diagnosis was well established as tuberculous pericarditis with caseous necrosis, death resulting mainly from cardiac failure.

Necropsy.—The heart and adherent pericardium weighed 2,000 Gm. (fig. 4). When the pericardial sac was opened, a fairly large amount of necrotic caseous material escaped from multiloculated cavities, the spaces of which were lined by grayish-white, shaggy, caseous tissue. The adherent pericardium was involved in a diffuse caseous tumor formation, which extended from the outer surface of the

Fig. 4 (case 5).—Massive tuberculous invasion of the entire heart. (The heart is viewed from the posterior aspect.) Note the pericarditis—the massive, caseous invasion of the right auricle and right ventricle, *C.T.*—and the narrow zone of remaining ventricular muscle, *m.* Note endocardial tubercles, *T*, and tuberculous ulceration, *T.U.*

pericardium into the depth of the underlying heart muscle. This process infiltrated all the chambers of the heart, particularly the ventricles, the thickened caseous wall measuring 35 mm. in various portions of the left ventricle and 50 mm. in the right ventricle. Demarcation between this process and the remaining cardiac

muscle was followed with difficulty because of the finger-like infiltration of the caseous mass into the myocardium. In some places the caseation reached the endocardium, causing localized swellings and ulcerations. Beyond the zone of active caseation, the adjacent muscle had undergone a grayish, gelatinous degeneration

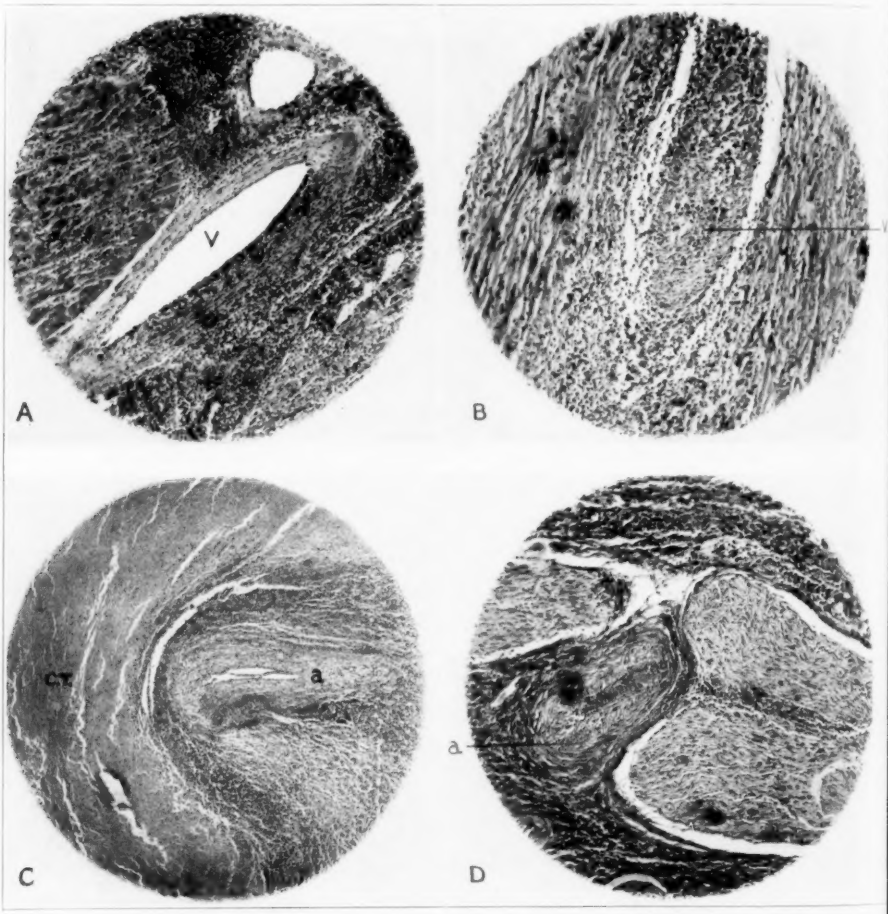

Fig. 5 (case 5).—*A*, diffuse tuberculous infiltration of entire wall of coronary vein, *V*; *B*, thrombosis and necrosis of the wall of the coronary vessel, probably a vein, *V*; *C*, diffuse intimal thickening of the coronary artery, leading to almost complete occlusion, *a*. Note the marked perivascular tuberculous infiltration and the massive caseation, which apparently compresses the artery, *C.T.*; *D*, small branch of coronary artery, *a*, showing diffuse intimal thickening and thrombosis.

to such an extent that in considerable portions of the heart, particularly in the right ventricle, there was no remaining cardiac muscle of normal appearance. The

papillary muscles and valves appeared to have escaped this invasion, although at the auricular-ventricular junction, caseation had extended into the valve rings.

The coronary vessels could be followed for only a short distance beyond their point of origin, being involved in and destroyed by the diffuse infiltration. No remnant of the main posterior descending artery or vein could be found, and the remaining portion of the left anterior descending artery could be followed for only a short distance from its point of origin. The portion of this vessel that was recognized showed a very narrow lumen and was flattened and compressed by the extensive surrounding tuberculous process.[5]

The mediastinal lymph nodes were markedly enlarged, white, soft and caseous. The pleura and the lungs showed no evidence of tuberculosis. The latter, however, were compressed by the enormous heart, and the right lower lobe contained numerous recent infarcts, probably the result of emboli composed of necrotic tuberculous material from ulcerations in the right auricle, which had occurred terminally. The spleen was large and firm (weight, 240 Gm.) and contained an infarction. The liver weighed 1,700 Gm., but showed no change except congestion, while the kidneys were not remarkable.

Histopathology.—Sections from the ventricles and auricles showed massive and widespread tuberculous pericarditis and myocarditis. The infiltration occurred as a wide zone of caseous necrosis and granulation tissue, which destroyed the outer portions and in some places the entire thickness of the myocardium. In general, from without inward, a cross-section of the heart showed the following distinct zones: an outer, yellowish-white zone, which was the widest and consisted of caseous necrosis; a middle zone, which was grayish and was made up chiefly of granulation tissue, and a brownish inner zone which consisted of the remaining undestroyed cardiac muscle. In the outer zone, small streaks of dark gray, gelatinous appearance indicated the course of blood vessels. Both the caseous portion and the zone of infiltration contained innumerable tubercle bacilli.

In many portions of the right auricle and in some parts of the left ventricle the myocardium was involved throughout its entire thickness. In some locations, a narrow subendocardial layer of muscle was still preserved, but even this was the seat of an acute interstitial myocarditis. This interstitial infiltration consisted of large and small foci of endothelial cells, lymphocytes, plasmocytes, typical Langhans' cells and occasional polymorphonuclears. Accompanying this infiltration were occasional tubercles. Where the focal collections were relatively large, caseation was present. The rich endothelial proliferation both in and around the small blood vessels in many ways suggested the pathologic involvement observed in rheumatic fever. (This will be discussed later.) The small vessels showed an endothelial hyperplasia, at times of such a degree as to cause almost complete obliteration of their lumens. In the subendocardial zone of undestroyed muscle that we are describing, the myocardium was comparatively well preserved except for areas in which cellular infiltration had progressed to the stage of local caseation. Even when surrounded by infiltrating cells, the individual fibers preserved their striation, stained fairly well and showed normal nuclei.

5. The means by which the existing heart muscle was nourished in the presence of almost complete destruction of the coronary arteries and veins is discussed in another paper (Bellet, S.; Gouley, B. A., and McMillan, T. M.: Nourishment of the Myocardium Through Thebesian Vessels in a Heart in Which the Large Coronary Arteries and Veins Were Destroyed by Tuberculous Myocarditis, Arch. Int. Med. **51**:112 (Jan.) 1933.

As already indicated, the coronary vessels were involved to an extreme degree, even the largest arteries being entirely destroyed. (As the other five cases also were subject to the same process to a lesser degree, tuberculous involvement of the coronary arteries will be considered as a whole elsewhere.)

The complete pathologic diagnosis was: tuberculous adhesive pericarditis; tuberculous myocarditis; tuberculous arteritis and arteriolitis, and destruction of coronary arteries and veins; tuberculous mediastinal lymphadenitis, and terminal miliary tuberculosis of the lungs and spleen.

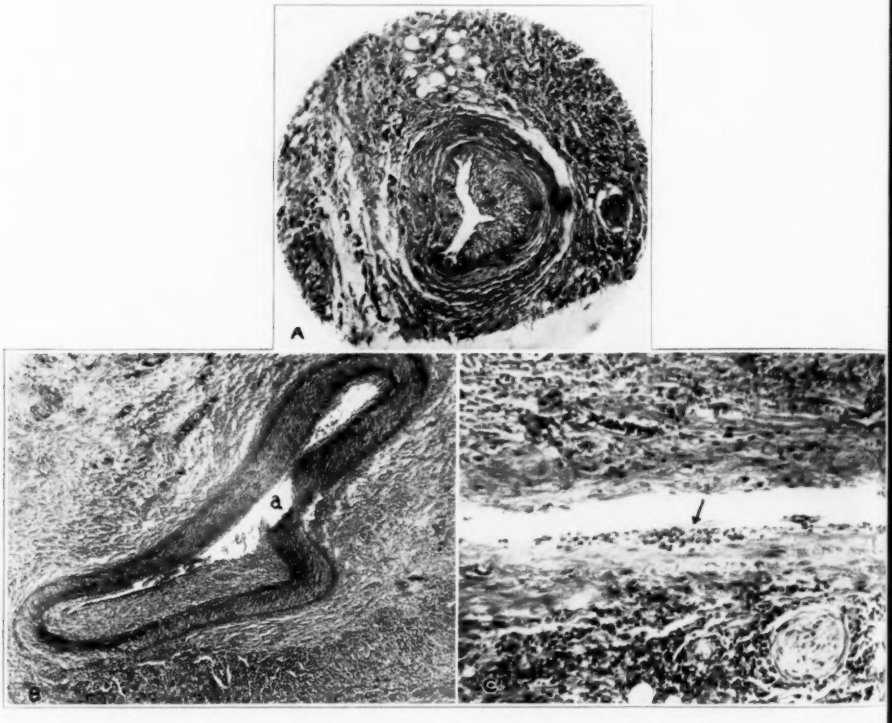

Fig. 6 (case 5).—*A*, branch of the coronary artery, showing typical "contact" tuberculous arteritis. Note the vacuolated noncellular thickening of the intima, leading to almost complete occlusion. *B*, posterior descending branch of the right coronary artery, *a*. Note the intimal thickening, in which there is mild cellular infiltration; most of this intimal proliferation appears, however, to be of the "contact" type. The media is not involved. *C*, intimal tubercle (marked with arrow) beneath endothelium of large vein.

Case 6.—*History.*—R. S., a colored girl, aged 16, was admitted to the wards for patients with tuberculosis of the Philadelphia General Hospital on Feb. 21, 1930, complaining of cough and pain in the lower left side of the chest, loss of weight and weakness. The patient was apparently in good health until January, 1930, when a heavy cold developed, which led to a persistent cough, progressive weakness

and a loss in weight of 25 pounds (11.3 Kg.). No history of hemorrhages or night sweats was obtained. The family and past histories revealed nothing of note.

Examination.—The patient was found to be considerably emaciated and extremely ill. Expansion over the right side of the chest was definitely limited, and evidences of consolidation of both lungs and cavitation of the right upper lobe were found. The only findings noted in the examination of the heart were slight enlargement and a systolic murmur at the apex. The abdomen and the extremities were normal.

Course.—From admission to death the patient had a continuous fever, ranging between 102 and 103 F. The pulse and respiration rates were 110 and 30 respectively. She gradually and progressively grew worse, until death occurred, on May 8, 1930. The clinical diagnosis was chronic ulcerative pulmonary tuberculosis.

Necropsy.—The heart was approximately of normal size, its weight being 180 Gm. There were a few small, discrete, tuberculous nodules and plaques over

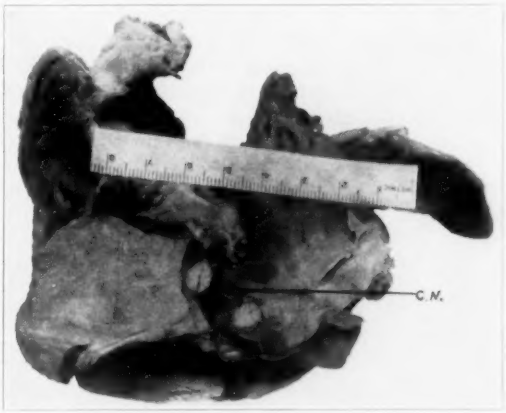

Fig. 7 (case 6).—Isolated caseous nodule, *C.N.*, in the wall of the pulmonary conus. There is no direct extension from the epicardium.

the right auricular appendage and the upper aspect of the left ventricle, and at the pericardial attachment to the great vessels. The epicardial lesions seemed definitely to follow the course of the blood vessels. They were small, and in no place were they observed to penetrate into the myocardium. There was, however, a firm, white, homogenous nodule, 1 cm. in diameter, situated in the right ventricular wall, just ventral to the pulmonary artery (fig. 7). This nodule projected into the lumen of the pulmonary conus but did not ulcerate. On its outer aspect a narrow zone of myocardium separated it from the epicardium. The myocardium throughout the rest of the heart showed only a mild pallor. The endocardium and valves showed nothing abnormal. The aorta and coronary vessels were normal.

The mediastinal lymph nodes were moderately enlarged, and were homogeneous and white on section. The central portion of some of these nodules was caseous. Both lungs showed a diffuse nodular tuberculosis with caseation, the left lung showing in addition tuberculous pneumonia involving the entire upper lobe. (The tuberculous involvement of other organs is indicated in the pathologic summary.)

Histopathology of the Heart.—In certain portions of the pericardium there were diffuse infiltrations of round cells, accompanied by small miliary tubercles. The latter appeared to be quite recent and showed a tendency to follow the course of the blood vessels. As far as we could ascertain, there was no connection or continuity between these epicardial infiltrations and the single nodule noted in the myocardium.

The nodule was definitely caseous, and surrounding it was a dense zone of epithelioid and round cells. It bulged considerably into the lumen of the right ventricle but was separated from the latter by a few stretched myocardial fibers, which had undergone pressure atrophy. A well preserved zone of myocardium was also present between the nodule and the epicardium. Except for that portion in the immediate vicinity of the caseous nodule, the muscle appeared to have preserved its integrity fairly well. An intensive infiltration of cells, chiefly endothelial and round cells, with scarcely any polymorphonuclears, was seen, but only in areas immediately adjacent to the solitary tuberculous nodule. In these same sites, edema, which in places presented an almost gelatinous appearance, was present between muscle fibers.

The large blood vessels showed no abnormalities. Intimal hyperplasia and tuberculous arteritis were not seen. Some of the small vessels, chiefly arterioles, showed a slight thickening of the intima. This was observed not only near the nodule but in fields somewhat distant from the tuberculous involvement.

The complete pathologic diagnosis was: tuberculous pericarditis and tuberculous myocarditis; diffuse nodular tuberculosis of the right lung and tuberculous pneumonia of the left lung, with ulceration of the lower lobe; tuberculosis of the mediastinal, retroperitoneal and mesenteric nodes, and tuberculous perihepatitis, serositis and enteritis.

COMMENT

Age.—In a series of 73 cases of myocardial tuberculosis collected from the literature by Anders,[3b] 40 per cent of the patients were less than 16, and 40 per cent were between 16 and 45. Only 5 of the 73 patients were above 60. Raviart[1] was able to collect from the literature 185 reported cases of myocardial tuberculosis, of which 182 were regarded by him as authentic. In 124 of these cases, only 23, or 18.5 per cent, were 40 years of age or older; 8 were between 60 and 70, and 4 between 70 and 80 years.

Site of Involvement.—Anders[3b] regarded the auricles as the chief site of tuberculous myocardial involvement, with the right auricle more commonly affected than the left. Raviart[1] regarded the left ventricle as the main site of involvement, but believed that the right auricle was the chief location of large tubercles.

Pathologic Classification.—Raviart[1] placed the cases he collected in groups showing the following conditions: (1) gross tubercles or nodules, (2) tuberculous infiltration or diffuse tuberculosis, (3) miliary granulation of the myocardium and (4) tuberculous myocarditis (interstitial, nonfollicular and parenchymatous myocarditis, without any other definite tuberculous cardiac involvement). Adopting and somewhat modifying this classification, we have placed the forms of tuberculous invasion of the cardiac muscle as we have observed it in our cases in

the following groups: (1) large tubercle, or caseous tumor (case 1), (2) tuberculous granulation infiltration (cases 2, 3 and 4), (3) widespread massive caseous tumor and granulation infiltration, a combination of types 1 and 2 (case 5) and (4) isolated small tubercle, occurring in the course of systemic miliary tuberculosis (case 6).

While all of our cases showed some degree of diffuse cellular interstitial myocarditis, in none of them was this the sole tuberculous lesion of the myocardium; it was clearly secondary.

The Manner in Which Tuberculosis Reaches the Myocardium.—A much simpler and, from the clinical point of view, perhaps as useful a classification of myocardial tuberculosis can be based on the location of the primary lesion and the manner of its spread to the heart. Such a classification would include only these divisions: (1) tuberculosis of the myocardium, resulting from direct extension from mediastinal glands—first to the pericardium and thence to the myocardium [6]—and (2) myocardial tuberculosis, resulting from dissemination by the blood stream of tuberculosis from some extracardiac focus.

According to such a simple classification, the first 5 cases of our series would fall under class 1. Our cases 1, 2, 3 and 4 represent the type and degree of involvement usually seen. Despite extensive glandular and pericardial lesions, the myocardial involvement consists only in the development of a large tubercle or group of several tubercles appearing as caseous tumors of moderate size with or without accompanying granulation tissue, being limited, in the 4 cases under discussion, to the right auricle.

The involvement shown in case 5, although differing from that seen in cases 1, 2, 3 and 4 only in degree and not in type, represents an extreme of infiltration that is rarely seen. Anders,[31b] in 1902, was able to find reports of only 2 cases of so extensive an involvement, and Raviart,[1] in his large series, only 12. The case recently reported by Thomson [31] was similar to our case 5, but did not present such extensive destruction.

When tuberculosis reaches the heart by direct extension, the mediastinal lymph nodes and not the lungs are considered to be the focus.

6. It is believed that tuberculosis of the pericardium and the myocardium can be caused by direct contact with an adjacent lymphadenitis: Kast (Ueber eitrige Pericarditis bei Tuberculose der Mediastinal Drüse, Virchows Arch. f. path. Anat. **96**:489, 1884) reported a case in which a caseous lymph node ulcerated into the pericardial sac. The normal lymphatic flow from the heart and pericardium is toward the mediastinal glands, and it is probable that when a pathologic condition in those glands results in lymphatic block, a reversal of the normal current takes place. Thus, with caseous tumor infiltrating the mediastinal and tracheobronchial lymph nodes, there is probably a reversal and eventual stagnation of the lymph flow, followed by establishment of tuberculous foci within the myocardium.

In our 6 cases, mediastinal involvement was present in all instances. In case 5, no evidence of pulmonary involvement, except terminal, was found, while in case 2, the only pulmonary lesion was a healed lesion the size of a ten cent piece. In case 3, there was no old pathologic condition of the lungs, the acute terminal miliary involvement being secondary to the myocardial tuberculosis. The remaining 3 cases did show widespread pulmonary tuberculosis.

We have placed our case 6 tentatively under the second heading of a classification based on the site of the original tuberculous focus and its mode of dissemination. We cannot positively consider that the isolated myocardial tubercle in case 6 had its origin in a blood-borne infection, because of the existence of tuberculous mediastinal glands and even more because of the few small epicardial tuberculous plaques. The type of tuberculosis in the lungs, spleen and other viscera, however, and the fact that the deep-seated isolated myocardial tubercle was separated from the epicardium by a zone of apparently healthy muscle, led us to feel that this lesion was in all probability blood-borne. The great resistance of the heart muscle to tuberculosis is illustrated by the rarity of myocardial involvement during miliary tuberculosis. In the case reported by Brockhausen [3h] the tuberculous infection did apparently reach the myocardium by the blood stream.

It should be borne in mind that myocardial tuberculosis may be the means of disseminating the disease and setting up a generalized miliary invasion. We believe this to have been the course of events in case 1. In this instance there was primary glandular tuberculosis, with secondary myocardial involvement, and a final generalized miliary invasion, the tubercle bacilli having escaped from the caseous tumor into the cavity of the right auricle through grossly visible ulcerations.

Primary Tuberculous Myocarditis.—In a few instances [3e, j, o] the myocardium has been reported to have been the sole site of tuberculous infection. The evidence presented is not conclusive.

Diagnosis.—Tuberculous myocarditis is probably more common than is generally believed. It not improbably is present in the form of slight infiltrating lesions in many cases of long-standing tuberculous pericarditis. It has been said that tuberculous myocarditis is a pathologic, rather than a clinical, entity, and that its diagnosis is rarely made in life. Tuberculous involvement of the myocardium probably does not result in the development of many symptoms or signs not present in pericardial involvement alone. The only diagnostic point we observed that we believe is suggestive of a myocardial tuberculous involvement is the development of ectopic rhythms in patients known to have tuberculous pericarditis. In case 5 (a boy, aged 16) auricular fibrillation was present continually for at least three months before death. In

case 2, a clinical diagnosis of this arrhythmia was made. In case 3 many auricular extrasystoles rather suddenly developed; after this the clinical course was downward. It seems probable to us that this disturbance of rhythm may have been the result of the extension of the pericardial process into the right auricular muscle. The observations of Fishberg,[7] in which the auricular fibrillation and flutter were frequently found to result from tumor metastases to the right auricle, are interesting in this connection.

The Similarity and Differentiation of the Interstitial Myocardial Involvement of Tuberculosis and Rheumatic Fever.—This similarity has been commented on before (Raviart[1] and Brockhausen[3h]). The resemblance results from the fact that in both of these myocardial lesions there is a perivascular cellular infiltration and an endothelial hyperplasia in small blood vessels leading to their occlusion. There are, however, certain features that enable one to differentiate these involvements. Tuberculous invasion is far more cellular and profuse, and is often accompanied by an edema that has a gelatinous appearance. In cases in which there is nodular formation the tuberculous lesion is often much larger than similar lesions seen in rheumatic myocarditis. Moreover, the variety of cells that constitute the Aschoff nodule is seldom seen in tuberculosis. Another important differentiating point is the fact that in tuberculosis the parenchymatous elements, in spite of marked interstitial changes, appear to suffer comparatively little; before the advent of caseation, the myocardial fibers are well preserved. In rheumatic myocarditis, in the active stages of the disease, there is usually seen marked parenchymatous degeneration of the muscle, although the interstitial infiltration may be comparatively sparse. Still another point of differentiation is the fact that involvement of the large coronary arteries to the extent seen in case 5 is rarely seen in rheumatic fever, and when present is of an entirely different type. In the latter disease arterial change is characterized by submiliary focal infiltrations of the adventitia and media, with small, patchy areas of destruction of the elastic tissue; the intima of the large coronary artery is scarcely ever involved to the point of imminent or complete occlusion.

Tuberculous Involvement of Coronary Vessels.—While tuberculous involvement of arteries is well known and has been frequently described in many organs, it has been observed but rarely in the heart, the only reported instances, as far as we are aware, being those of Brockhausen,[3h] Thomson[3t] and Pic and Morénos.[3s] In their cases, involvement was confined to smaller arteries. In 5 of our cases (cases 1, 2, 3, 4 and 6) only small vessels were affected. In case 5, however, the

7. Fishberg, A. M.: Auricular Fibrillation and Flutter in Metastatic Growth of Right Auricle, Am. J. M. Sc. **180**:629, 1930.

tuberculous involvement included the very largest divisions of the coronary arteries and in this respect as well as in the type of involvement observed is unusual.

Three types of involvement of the coronary vessels were seen: (1) formation of intimal tubercles; (2) tuberculous invasion of the adventitia with focal or diffuse involvement of the entire wall, and (3) noncellular thickening of the intima, which, if sufficiently extensive, may lead to vascular occlusion. In cases 1, 2, 3, 4 and 6, only the latter form was seen; in case 5, all of these types of arterial involvement were observed. Only in case 5 were veins as well as arteries affected.

In case 5 many vessels showed small collections of lymphocytes and endothelial cells in the intima (intimal tubercle), as can be seen in figure 6; such intimal invasion in places involved the entire circumference of the vessel (the circular intimal tubercle of Askanazy[8]). The media and adventitia of a vessel showing intimal tubercle formation often appeared to be normal, and we must conclude that the intimal tubercles in such instances had their origin in a blood-borne infection (through the coronary circulation).

Tuberculous invasion of the adventitia with focal or diffuse involvement of the entire wall was seen in both medium and small sized arteries and veins in case 5 (figs. 5 *A* and *B*). This type of invasion always occurred in the midst of surrounding tuberculosis, being the result, therefore, of a direct extension from an adjacent perivascular tuberculous lesion.

In case 5 almost all the arterial branches, even in the absence of definite cellular invasion, showed thickening of the intima. This consisted of swelling of the subendothelial tissue, unaccompanied by cellular infiltration; it apparently was not the result of cellular hyperplasia. The process had the appearance of an edematous thickening with vacuolization of fibrous tissue. This type of involvement was seen best in the large arteries, though arterial branches of various sizes were affected (fig. 6 *A*). Occasionally, in the larger vessels, the media was likewise swollen, the muscle cells vacuolated and the distinction between media and intima lost, for both had a spongy appearance. The intimal thickening either involved the entire circumference of the vessel or was localized and projected into the lumen as a rounded knob. The lining endothelium was intact. The lumens of involved vessels were narrowed and in some instances completely closed by an approximation of the intimal surfaces or by the formation of a thrombus. This type

8. Askanazy, quoted by Jores, L., in Henke, H., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie: II. Herz und Gefässe, Berlin, Julius Springer, 1924.

of involvement has long been recognized in the lung and may be called "contact endarteritis."[9] The condition has a characteristically spongy and vacuolated appearance. It is distinct from the intimal tubercle in that it is noncellular and is apparently not dependent on the presence of tubercle bacilli in the intima (fig. 6*A*). (We have occasionally seen it in syphilis, and it may possibly occur in other infections.) In many locations the lumens of already thickened blood vessels were further narrowed by compression of surrounding caseous masses (fig. 5*C*). The proximal portions of the large coronary arteries, although surrounded by caseation, were enclosed within jackets or islands of cellular infiltration having a gelatinous aspect. Before some of the large vessels became completely destroyed, lumens were rendered slitlike by compression and intimal thickening.

SUMMARY

1. Six cases of tuberculosis of the myocardium are reported, the ages of the patients being 16, 16, 26, 46, 51 and 72 years. Four were male, and 2 were female; 4 were Negroes, and 2 were white people.

2. These cases represent the different types of tuberculous myocarditis that have hitherto been reported. A simple classification is suggested, based on the mode of dissemination and the type of lesion: (*a*) myocardial tuberculosis, secondary to mediastinal glandular and pericardial tuberculosis, and (*b*) as part of systemic miliary tuberculosis.

3. Involvement of the coronary arteries, in one case to an unusual degree and in the other cases to a slight degree, is reported, and the various types of tuberculous arteritis are described: (*a*) diffuse tuberculous arteritis, involving all the vessel coats; (*b*) intimal tubercle without involvement of other vessel coats, as a result of blood-borne infection, and (*c*) a type of arterial involvement by tuberculosis (contact arteritis) previously not described in the heart, affecting not only the small, but also the large, coronary arteries and leading to narrowing of their lumens and even to complete occlusion.

4. The occasional similarity of rheumatic and tuberculous myocarditis is noted, and a differential diagnosis is outlined.

5. The probability of ectopic rhythm, resulting from the tuberculous infiltration of the right auricle, is discussed.

The following chiefs of service, Drs. C. A. Aitken, Robert G. Torrey, Edward A. Strecker, Joseph McIver and John McLean, and the following pathologists, Drs. Morgan, Robson, Bortz, Yinger and Custer, permitted us to report these cases.

9. This type of intimal hyperplasia has been observed in the smaller arteries in the vicinity of tuberculous infiltration in other organs, notably the lungs and meninges. It may be called "contact endarteritis" (Opie, E.: Personal communication).

PARADOXICAL BREATHING

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Paradoxical breathing means the deflation of a lung or of a portion of a lung during the phase of inspiration and the inflation of the lung during the phase of expiration.

Paradoxical breathing occurs in all air-breathing vertebrates. It depends on the same anatomic factors as the residual air and seems to serve the same purpose.

DATA FROM COMPARATIVE PHYSIOLOGY

During the evolution of the air-breathing apparatus, provisions were necessary for the dilution of the oxygen of the air,[1] and for its saturation with moisture. In the water, where the amphibian ancestors of modern man lived, the concentration of oxygen is less than 1 per cent; in the atmosphere the concentration is nearly 20 per cent. Among the morphologic adaptations to air breathing, the following are of interest:

1. The respiratory passages become long and narrow; a constriction develops in the air tube (the glottis), which narrows in expiration. This arrangement leads to the accumulation of residual air in the lungs.

2. Respiratory movements occur with the glottis and nares closed, directly bringing about an interchange of air between the several portions of the respiratory tract. In the adult amphibians the normal respiratory cycle consists of: (*a*) Aspiration. Air is sucked in from the atmosphere into the mouth and pharynx, with the nares open and the glottis closed. (*b*) Expiration. The glottis opens, and the nares close; stale air escapes from the lungs into the mouth and mixes with the fresh air therein. (*c*) Inspiration. The muscles of the mouth and pharynx contract and press the air mixture into the lungs. Frogs thus always breathe impure air, and their lungs are protected from the dry atmospheric air rich in oxygen. In reptiles the respiratory cycle consists of: (*a*) inspiration; (*b*) expiration with the glottis open, and (*c*)

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1. Keith, Arthur: Respiration in Frogs, Nature **69**:511, 1904. Jordan, M. J.: Allgemeine vergleichende Physiologie der Tiere, Berlin, W. de Gruyter & Co., 1929, p. 132.

expiration with the glottis closed. During the last mentioned phase an exchange of air occurs between the membranous air sac and the lung proper. This third stage of reptilian respiration is of life-saving importance in snakes, in which the trachea may be compressed for hours during the prolonged act of swallowing large objects.

In birds, an interchange of air between the lungs and air sacs also occurs physiologically (and is of vital importance during the act of flying when the chest must be kept rigid).[2]

In the human new-born baby the first expiration (the first cry) is accompanied by a contraction of the glottis. The air drawn into the lung with the first inspiration is but partly expelled into the atmosphere: a portion of the inspired air is entrapped in the infundibula (residual air); another portion is pressed, via the bronchial intercommunications, into the apical and mediastinal portions of the lungs (paradoxical breathing).

In birds and reptiles the air sacs are supplied by the systemic circulation; the contained air is not vitiated as the systemic blood is not oxygenated. In mammals, the air sacs have been incorporated into the lungs proper; all portions of the lungs are traversed by the pulmonary blood vessels. Residual air and paradoxical breathing in mammals mean breathing of stale air. The mammals have become well adapted to atmospheric air, but the anatomic structures leading to residual air and rebreathing have persisted and are of doubtful utility. In labored breathing, the result of effort, and in dyspnea resulting from disease of the heart or lungs, the residual air and paradoxical breathing increase the undesirable symptoms. Under certain conditions the symptoms caused by paradoxical breathing may dominate the clinical picture and may be the immediate cause of death (in open pneumothorax, for example).

Absence of True Muscles of Respiration.—In this connection it must be pointed out that in human beings no specialized muscles of respiration have developed in the sense that the heart muscle is specialized for the circulation of the blood. In fishes and young amphibians the muscles of the mouth carry on the ventilation. The water is taken in through the mouth and is poured out through the gill clefts by a contraction of the pharyngeal pump mechanism. In reptiles, birds and mammals the muscles of the chest and abdomen find increasing use in respiration, as the muscles of the head and neck gradually lose their importance. In turtles, in which the chest and abdomen are rigid, the muscles of the shoulder and pelvic girdles carry on the respiration. In mammals the diaphragm has become a muscular structure; owing to the migration of the lung into the chest cavity the diaphragm comes to lie between the

2. Babak, E., in Winterstein: Handbuch der vergleichenden Physiologie, Jena, Gustav Fischer, 1911, vol. 1, pt. 2, p. 911.

chest and abdomen in such a way that its contraction enlarges the chest. In mammals the diaphragm thus becomes an important muscle of respiration, owing to its favorable location. In the lower vertebrates the diaphragm has a circulatory function only.[3] It is thus evident that all the muscles of the face, neck, chest, abdomen, spine and extremities may be employed as muscles of respiration. During tranquil breathing, the nerves to the intercostal muscles alone are stimulated; for more active breathing the nuclei of the nerves to the diaphragm and to the scalene muscles are also irritated; in cases of dyspnea all the muscles of the body may be called into use for the ventilation of the lungs.

Antagonism Between Functions of Locomotion and Respiration.—About the time that lungs were being developed in vertebrates for air breathing and the body musculature was being adapted for ventilation of the lungs, extremities began to develop for locomotion on land. The muscles of the trunk were now requisitioned for uses other than ventilation of the lungs. The chest had to become more rigid in order to protect the viscera from the weight of the animal, which increased as the buoyancy of the water was lost; more rigidity was also necessary to give the muscles of the extremities power to contract. With the specialization of the upper extremities for flight, climbing, manual labor and other functions, the respiratory capacity of the chest was further encroached on. Not only do there occur permanent ossification and consolidation of the portions of the sternum and ribs, but for increased efficiency of the muscles attached to the chest, the efforts of straining, lifting of weights, etc., are made with respiration entirely suspended (generally after inspiration and closure of the glottis). The muscles of the shoulder and pelvic girdles, taking origin from those of the chest, may now contract, the chest remaining rigid and being kept from collapsing by the air entrapped in the lungs. During this activation of the muscles of the chest with the glottis closed, an interchange of air occurs between the different portions of the lungs.

PARADOXICAL BREATHING IN HUMAN BEINGS

Physiologic Considerations.—The interchange of air between the different portions of the lungs is rendered possible by the following circumstances:

1. The interbronchial communication between the two lungs is short as compared with the distance between either main bronchus and the source of fresh air at the mouth or nares. The interbronchial space remains patent under all physiologic conditions, while the communication with the atmosphere is frequently abolished by the narrowing or closing

3. Keith, Arthur: The Nature of the Mammalian Diaphragm, J. Anat. & Physiol. **39**:261, 1904-1905.

of the glottis. The obstruction to the atmospheric air may, moreover, be produced at the lips and nares, as in breathing through a mask, whistling, glass blowing or playing of wind instruments.

2. In inspiration, the trachea and bronchi elongate and their lumen increases; in expiration, the respiratory passages shorten and become narrow, the narrowing affecting particularly the glottis. This coordination of the voluntary muscles of the chest and the involuntary bronchial muscle has been ascribed to the action of a respiratory center. However, as Howell [4] pointed out, there is an inspiratory center only. Expiration depends largely on the force of gravity and on the elastic recoil of the lungs. In forced expiration of dyspnea there may occur a spasmodic contraction of the bronchi and glottis partly defeating the purpose of expiration. The antagonistic action of the expiratory abdominal muscles and of the bronchial muscles has long been known from clinical observations. Recently this condition has been demonstrated by means of electrobronchograms.[5] In forced expiratory movements, owing to obstruction at the glottis, air is driven from the more active to the less active portions of the chest.

3. The chest is not uniformly supplied with musculature, and the different regions of the chest differ in their respiratory capacity. Thus the apical region is relatively deficient in muscle, and there is no muscle tissue available to actuate the mediastinal portions of the lungs. Roth [6] and also Metzger and Auer [7] have shown that the intrapleural pressure varies in the different portions of the chest, and that its respiratory fluctuations are greater in the basal portions. In the less active regions of the thorax the pressure relations are nearly those of the atmosphere in both phases of respiration, while in the more active portions the pressure falls in inspiration and rises in expiration. During deep inspiration, air is sucked into the active portions of the lungs not only from the trachea but from the inactive portions of the lungs; during forced expiration, air is expelled not only into the atmosphere but into the inactive portions of the lungs. This inflation of the lungs during expiration is favored by the narrowing of the glottis and trachea accompanying forced expiratory and straining efforts.

4. The ribs are attached to the spine at such an angle that enlargement of the chest, or inspiration, is possible only by elevation of the

4. Howell, W. H.: Textbook of Physiology, ed. 11, Philadelphia, W. B. Saunders Company, 1930, p. 713.

5. Luisada, Aldo: La contractilité active du pulmon, etudiée au moyen de l'électro-bronchographie, Arch. méd.-chir. de l'app. respir. **5**:320, 1930.

6. Roth: Regarding Intrapleural Pressure, Beitr. z. Klin. d. Tuberk. **4**:437, 1905.

7. Metzger, S. J., and Auer, John: The Respiratory Changes of Pressure at the Various Levels of the Posterior Mediastinum, J. Exper. Med. **12**:34, 1910.

ribs. Any movement of the body or any posture which results in an elevation of the ribs produces an enlargement of the chest. Stretching of the arms and extension of the spine mean inflation of the lungs, provided the glottis is open. If these movements are performed with the glottis closed, there will occur an interchange of air between the several portions of the lungs. In the erect posture the ribs are inclined downward, the chest is in relative expiration, and there is less residual air in the lungs; in the recumbent position the ribs are more horizontal and the lungs are in relative inspiration. When the subject lies on one side or leans to one side, the lower hemithorax is in collapse, its lung being relatively airless, while the upper half of the chest is enlarged and its lung is emphysematous. When the subject leans now to one side, now to the other, with the breath held, one can plainly observe under the fluoroscopic screen the escape of air from the lower into the upper part of the lung. This paradoxical breathing can be readily confirmed by physical examination.

5. Normal respiration in the higher vertebrates depends on a drop of air pressure in the lungs with the inspiratory enlargement of the chest, so that air is admitted under atmospheric pressure, and an increased air pressure in the lungs in expiration, expelling stale air into the atmosphere. The atmospheric pressure on the chest wall is overcome by the rigid ribs and by normal muscle tone. In case of injury to the ribs or muscles, as after thoracoplastic operations or in rickets, the softened portions of the chest respond to atmospheric pressure in the same manner as the atmospheric air; i. e., during inspiration the tissues are pressed inward, and during expiration they are pressed outward (paradoxical movement). Thus, during the same phase of respiration, the pressure may be increased in one portion of the chest and decreased in another portion, leading to an interchange of air and other fluid materials.

PARADOXICAL BREATHING IN HEALTH

Paradoxical Breathing in the Apexes of the Lungs.—The apex of the lung, situated above the level of the anterior end of the first rib, is exposed to atmospheric pressure, the thoracic wall being deficient in bone and muscle in this region. With the fall in intrapleural pressure during deep inspiration the weight of the air on the outside of the chest compresses the unprotected apex of the lung in the same manner as it presses air into the trachea. With the rise of intrathoracic pressure above atmospheric pressure during forced expiration, the apex bulges out, there being no ribs or strong muscles in this region of the wall of the chest. The more labored the breathing the more pronounced is this paradoxical excursion of the apex, which can be observed by direct inspection and by roentgen examination.[8] In apical pleuritis and in

8. Kreutzfuchs, S.: Radiological Examination of the Lung Apices, München. med. Wchnschr. **59**:80, 1912.

infiltrations associated with airlessness and bronchial occlusion, the paradoxical breathing is less pronounced or absent. In fluoroscopic examination of the chest the "normal" paradoxical behavior of the apex is looked for before tuberculosis is ruled out.

In complete unilateral pneumothorax, the air content of the apical region also diminishes in inspiration and increases in expiration; this shows that the paradoxical behavior of the apex depends on the structure of the thoracic wall rather than on the architecture of the lung.

Paradoxical Breathing in the Mediastinal Portions of the Lungs.—During the expiratory efforts of coughing, straining and similar acts, the mediastinal portions of the lungs are inflated; the sternum and contiguous parts are elevated, and the upper four or five interspaces may bulge out (Tendeloo[9]). The upper three or four intercostal spaces increase in a vertical direction, as can be demonstrated by roentgenograms made during the two phases of respiration. This paradoxical behavior of the mediastinal and apical portions of the lungs is more pronounced in emphysema and is etiologically related to the production of emphysema.

CASE 1.—The clinical diagnosis was chronic fibrosis and emphysema of the left lung following a gunshot wound. Roentgenograms of the chest made in inspiration and in expiration yield the following information: In expiration the right base has collapsed much better than the left; the apexes have become inflated during expiration. The first intercostal space is wider in expiration. The transverse diameter of the lungs is increased in expiration, encroaching on the mediastinal shadow. At the level of the third cartilage on the left side there is a foreign body in the anterior portion of the mediastinum, vaguely showing in inspiration; in expiration this body is well defined, owing to the inflation of the surrounding lung in expiration. On the right side the mediastinal portion of the lung is also better inflated in expiration (fig. 1 *A* and *B*).

CASE 2.—The clinical diagnosis was fibroid tuberculosis of the left lung of fifteen years' duration.

Stereoscopic examination of films made in inspiration shows the left lung and chest to be contracted in all directions. There are many star-shaped fibrous deposits in the upper half of the left lung. The root of the left lung is displaced upward and outward. There is a large transparent area with a convex outer border to the left of the aortic knob; it is the mediastinal portion of the right lung which has hypertrophied and has invaded the left hemithorax. Films made in expiration show the usual deflation of the bases and inflation of the apexes. The mediastinal "lung hernia" has enlarged in expiration.

The mediastinal ballooning frequently occurring in artificial pneumothorax is also more marked during the phase of expiration.

The vicarious inflation of the apical and mediastinal portions of the lungs becomes pronounced during labored breathing associated with

9. Tendeloo, N. P.: Studien uber die Ursachen der Lungenkrankheiten, ed. 1, Wiesbaden, J. F. Bergmann, 1902, p. 55.

severe exertion, as in track runners. The increased oxidation caused by the activity of the muscles demands labored breathing. The inspirations are deepened, and the expirations are forced and prolonged owing to the narrowed glottis; the abdominal expiratory muscles are brought into play. Air is driven with supra-atmospheric pressure from the basal into the apical and mediastinal portions of the lungs.[10] During the labored inspiration, air is taken in not only from the atmosphere but from the apical and mediastinal portions where the pressure may be above atmospheric. Owing to the increasing venosity of the blood, the respirations are increasingly more labored and more frequent, so that the lungs are soon overinflated, largely with stale air (volumen pulmonum acutum).

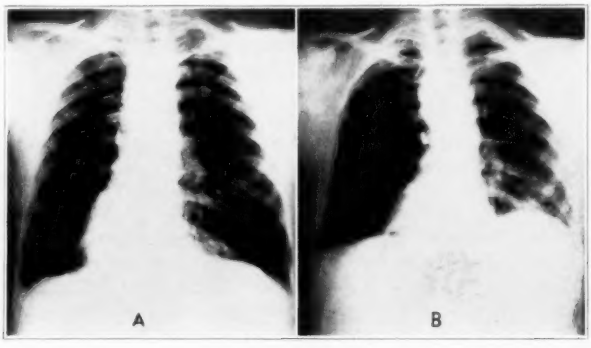

Fig. 1 (case 1).—*A*, inspiration. *B*, expiration. The basal portions are deflated, and the apical and mediastinal portions are inflated during expiration. The foreign body in the left anterior mediastinal portion of the lung is rendered conspicuous by the inflated lung in expiration.

The Litten Phenomenon.—In the lower lateral aspect of the chest, where the interspaces are wide and the muscle is relatively thin, there normally occurs a sinking in of the interspaces during inspiration. As the intrapleural pressure falls in inspiration, the weight of the outside air immediately presses in the soft tissues; the action of the atmospheric air through the lungs is weakened by the friction the air encounters in the long and narrow bronchi. The inspiratory retraction of the interspaces occurs simultaneously with the contraction of the diaphragm but is independent of it. The Litten phenomenon may be observed in cases of dyspnea, even if the diaphragm is paralyzed.

10. Fici, cited in letter from Italian correspondent, J. A. M. A. **98**:157 (Jan. 9) 1932.

The Harrison groove appearing in thoracic walls with soft ribs (in rickets) also develops in the same region of the chest and is due to the same factors.[11]

PARADOXICAL BREATHING IN DISEASE

Open Pneumothorax.—In this condition paradoxical breathing has been described repeatedly, both in the human subject and in the experimental animal.

In the adult the lung is smaller than the cavity of the chest, and it is kept stretched by atmospheric pressure into apposition with the thoracic wall; this wall is compressed by atmospheric pressure into contact with the lungs. The pressure conditions in the potential pleural space are subatmospheric. If an opening is made into the pleural cavity and air is allowed to act on the lung under atmospheric pressure, the wall of the chest immediately expands;[12] the lung retracts from the wall and can no longer follow the respiratory movements of its hemithorax. Through the bronchial connections with the other lung, it responds to the activity of the opposite hemithorax. During each inspiration the intact lung sucks in air not only from the trachea but from the relaxed lung; during expiration it expels a portion of its air into the functionless lung. The healthy lung thus breathes a mixture of stale and fresh air. The stale air reaches the alveoli first, as the bronchus of the collapsed lung is shorter than the upper respiratory tube. The blood soon becomes venous, and cyanosis and dyspnea are marked; the respirations are forced, the expirations are prolonged, and the abdominal muscles are brought into play. This is associated with narrowing of the glottis (see page 267) which means that more of the air current is diverted into the passive lung. During each violent inspiration the lung in which the pneumothorax is present collapses and the atmospheric pressure displaces the heart toward the healthy side; during the succeeding forced expiration the pressure in the healthy lung is raised considerably above atmospheric, and the heart is displaced toward the opposite side as the passive lung is ballooned out; it may be brought in contact with the wall of the chest or even be pushed through the wound. The suction force of the healthy side is thus largely spent in aspirating the mediastinum instead of in drawing in air from the trachea; conversely, some of its expiratory force is absorbed by the displacing of the mediastinum. Should the mediastinal septum be rigid, owing to inflammatory adhesions, the healthy lung will be less embarrassed in its action. Fixing of the mediastinum by manual traction relieves the dyspnea and cya-

11. Gray, Henry: Anatomy, Descriptive and Surgical, new American edition from the eighteenth English edition, Philadelphia, Lea & Febiger, 1913, p. 237.

12. Bert, Paul, in Leçons sur la physiologie comparée de la respiration, Paris, J. B. Baillière et fils, 1870.

nosis;[13] conversely, pressure on the abdomen, by relaxing the mediastinal attachments, increases the distress. Producing an artificial opening in the trachea relieves the symptoms[14] by shortening the respiratory passages and by obviating the narrow glottis.

Placing of the subject on the wounded side causes some relief,[15] the mediastinum becoming fixed by its own weight (case 3, page 275).

Hernia of the Lung.—It is now well known that in hernias of the lungs the breathing is paradoxical. Cloquet, in 1817, noted that in inspiration the hernia disappeared; in expiration it bulged out. Wahl[16] succeeded in demonstrating a hernia of the lung in a roentgenogram (the plate was made during straining expiration with the glottis closed).

Asthma.—In bronchial asthma there is a spasmodic narrowing of the bronchi and glottis, more pronounced in expiration. There are increased resistance to the outflow of air and rapid accumulation of residual air. With each expiration air is driven from the basal and lateral portions of the chest into the apical and mediastinal regions.[17] This rebreathing is largely responsible for the respiratory distress and cyanosis.

Emphysema.—In pulmonary emphysema there is increased residual air. The portions of the lungs affected earliest and most extensively are the apical and mediastinal regions.[18] It is easy to see why in bronchitis and laryngitis with chronic cough there should develop overdistention of these poorly muscled regions of the lung, by a process of paradoxical breathing. During each paroxysm of coughing air is blown into the mediastinal and apical portions of the lungs. This is also true of occupational emphysema, i. e., the emphysema following the practice of occupations entailing sustained respiratory efforts (for instance, glass blowing, singing and playing of wind instruments).

In emphysema developing in persons not engaged in strenuous occupations and without primary bronchitis, it is believed that the respiratory passages are naturally longer and narrower than usual (Tendeloo[19]) or that there is an exaggerated narrowing of the glottis in expiration. In such persons ordinary talking and moderate manual labor may bring

13. Sauerbruch, E. F.: Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1925, vol. 1, p. 603.

14. Dwyer, J. O.: A Few Vivisection Experiments, Loomis Laboratories, University of the City of New York, 1890, p. 53.

15. Ewald, Carl: Ueber das Mediastinalflattern, Wien. klin. Wchnschr. **39**: 697, 1926.

16. Wahl, Reed: Zur Klinik und Roentgenologie der Lungenhernie, Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:670, 1929.

17. Hofbauer, Ludwig: Asthma, Berlin, Julius Springer, 1928, p. 11.

18. Lord, F. T.: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1915, p. 150.

19. Tendeloo, N. P.: Studien über die Entstehung und der Verlauf der Lungenkrankheiten, ed. 2, Wiesbaden, J. F. Bergmann, 1931, p. 71.

about as much paradoxical breathing and as great an accumulation of residual air as occur in more normal persons only from acts associated with severe expiratory efforts.

Tuberculosis and Other Infections.—In pulmonary tuberculosis, bronchiectasis, pneumonia, pulmonary abscess and other infections of the lungs, there occurs an interchange of air and of infectious material between the various portions of the lungs, generally during coughing spells and during straining efforts. This paradoxical breathing is responsible for the interbronchial spread of tuberculous and other infections in the lungs and for the condition known as migratory pneumonia. During roentgen examination of patients after injections of iodized poppy seed oil 40 per cent, the spread of the oil from one lung into the other and from a lower lobe to an upper lobe bronchus has been frequently observed. During operations on the chest for tuberculosis or other infections, if paradoxical breathing occurs, owing to resection of the ribs or to open pneumothorax, there is grave danger of spreading of the infection in the lungs.[20]

The prognosis in tuberculosis and bronchiectasis is better for persons of sedentary occupation, for the reason that these persons do not engage in strenuous muscular effort, with the concomitant paradoxical breathing (expiratory effort, with the glottis closed).

The paradoxical excursions of the wall of the chest overlying a tuberculous process can frequently be observed by inspection.[21] Elsewhere I have presented roentgenographic illustrations of paradoxical breathing in tuberculous cavities [22] and in atelectatic lungs.[23] Paradoxical breathing has been described as the cause of cyanosis and dyspnea in pneumonia.[24] The bottle-blowing exercises employed in the postoperative treatment of empyema are also of interest in this connection.

Extensive Operations on the Wall of the Chest.—After these operations paradoxical breathing nearly always occurs, occasionally causing more disability than the condition for which the operation was performed. The paradoxical breathing is more marked if the anterior portions of the ribs are removed, as in this portion of the chest the interspaces are wide and there is less muscle to protect the lung from atmospheric pressure that there is in the back of the chest. If the

20. Davies, H. Morriston: Surgery of the Lung, New York, Oxford University Press, 1930, p. 33.

21. Fishberg: Pulmonary Tuberculosis, ed. 3, Philadelphia, Lea & Febiger, 1922, p. 308.

22. Korol, E.: Atelectasis in Pulmonary Tuberculosis, Am. Rev. Tuberc. **23**: 505 (May) 1931.

23. Korol, E.: Etiology and Mechanics of Massive Atelectasis, Am. Rev. Tuberc. **24**:284 (Sept.) 1931.

24. Duken: The Significance of X-Ray Examination in Pneumonia, Monatschr. f. Kinderh. **41**:174, 1928.

pleura is thickened and the mediastinum is fixed, there is less respiratory distress.

Following operations on the left side of the chest, the to-and-fro movement of the heart with respiration may be seen; during inspiration the heart is pulled to the right and becomes invisible; during expiration a large area of pulsation is seen to the left of the sternum (case 3). If the observer takes hold of the costal stumps and forcibly resists their collapse with inspiration, the patient's respiratory distress is diminished and the paradoxical action of the underlying lung disappears, as well as the flopping of the heart. The vital capacity of the patient improves markedly when the wall of the chest is supported so that its paradoxical movement is abolished.

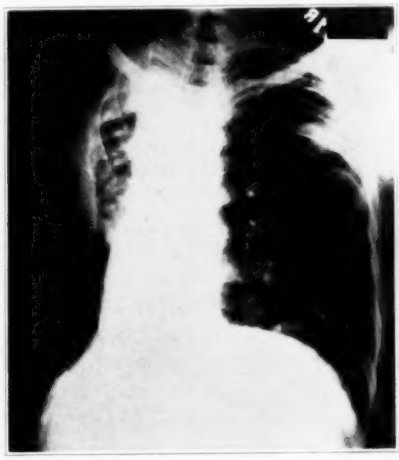

Fig. 2 (case 3).—Extent of the resection of the left hemithorax. Considerable air-bearing tissue remains in the left lung.

Case 3.—During the months of February and March, 1926, a man underwent an extensive thoracoplastic operation on the left side of the chest, in four stages, for the treatment of tuberculous pyopneumothorax. Portions of the upper eleven ribs were removed paravertebrally; in addition the axillary portions of the seventh, eighth, ninth and tenth ribs were resected through an incision in the anterior axillary line. The patient recovered gradually, and for two years enjoyed fair health.

In the spring of 1929, a cough developed, the patient began to lose weight, and there was marked dyspnea on exertion.

In June, 1929, the condition of the lungs was as represented in figure 2, with physical signs of cavity in the lower lobe of the right lung and tubercle bacilli in the sputum. Shortness of breath was the principal complaint. The paradoxical movement of the left lung was spectacular. The extensive thin, hairless scar in the left axilla, through which the blue lung could be seen, was deeply retracted

with each inspiration and bulged out with each expiration, fairly ballooning out with each cough and straining movement. The heart could be seen over a large area during expiration; it became invisible behind the sternum during inspiration. The larynx also moved to the right in inspiration and to the left in expiration. The patient rested on his left side continually, and decubital ulcers had developed on the stumps of three of the ribs. When the examiner took hold of the sternal stumps of the ribs and held up the thoracic wall, resisting the atmospheric pressure on the ribs in inspiration, the patient immediately volunteered the statement: "This feels good. I can breathe fine this way." During this maneuver the movement of the left lung was greatly limited and the migrations of the heart and of the larynx disappeared. The vital capacity was 1,200 cc. When the sternum was held up to resist the paradoxical movement, the vital capacity rose to 1,525 cc.

There were increasing dyspnea and cyanosis. Edema of the legs appeared, and later ascites and enlargement of the liver. There were no heart murmurs. The patient did not like to be propped up on pillows, but preferred to rest on the left

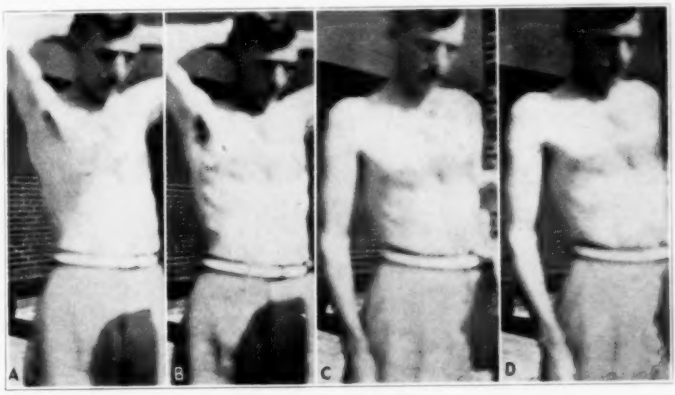

Fig. 3 (case 4).—*A*, inspiration. The left side of the chest is contracted in inspiration. *B*, expiration. The left side is larger than in *A* (paradoxical breathing). *C*, inspiration with the rib stumps supported against atmospheric pressure; the left side now moves normally. *D*, in expiration the left side is now smaller than in *C* and *B*.

side (see page 272). Over two of the rib stumps the tissue sloughed away, and dead white bone was exposed. Inhalations of oxygen relieved the dyspnea and cyanosis, but just as much relief was obtained from manually pulling up on the rib stumps.

The following is an abstract of the protocol of the autopsy, dated Aug. 15, 1929: There was a large amount of fluid in the peritoneal cavity. The liver was congested, and the spleen enlarged. There was much clear fluid in the pericardial cavity. The right lung showed extensive changes of tuberculosis with formation of cavities. The left lung consisted of several rather solid, flat, tonguelike processes which were adherent to the operative scar, the diaphragm, the pericardium and the cupola of the pleural cavity. Air-bearing tissue was present in the anterior portions of this lung. On section this lung was described as consisting of congested areas of collapsed lung, alternating with gray caseous deposits.

It will be seen that the lesions in the left lung were not healed three years following the extensive thoracoplasty. Undoubtedly the healing was disturbed by the paradoxical breathing which, during labored breathing, exceeded 20 per cent of the total (see the vital capacity figures). The air current between the two lungs probably carried the infectious material from the left into the right lung.

Death from heart failure was described in these cases by Bruns.[25]

Case 4.—During the summer of 1929 a man underwent three operations for recurrent empyema. The eighth, ninth, tenth and eleventh ribs were resected subperiosteally, from the posterior axillary line to near the cartilaginous ends on the left side. The empyema was cured, and the patient recovered, with much deformity of the chest wall. There was a cup-shaped depression in the lower part of the left axilla which became deeper on inspiration and was nearly obliterated on expiration. When the left costal arch was supported in such a way as to resist the

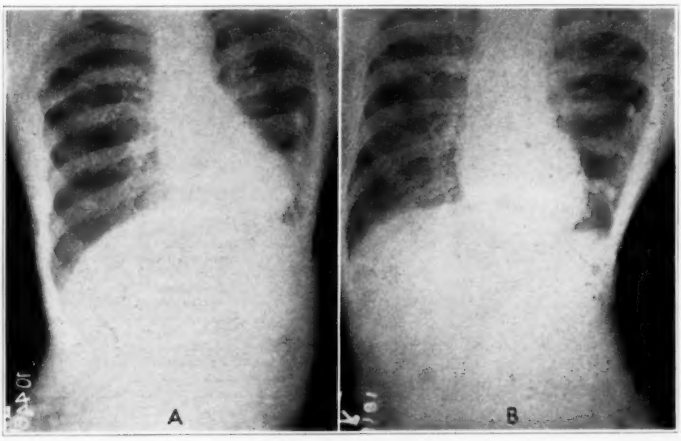

Fig. 4 (case 4).—*A*, inspiration. Note collapse of the base of the left lung. *B*, expiration. The base of the left lung is inflated in this phase of respiration (paradoxical breathing).

collapse of the chest during inspiration (fig. 3 *C* and *D*) the man stated that he felt better and could breath more freely. The vital capacity on Dec. 18, 1929, was 1,500 cc., and 1,900 cc. with the left side of the thoracic wall supported. In October, 1931, the vital capacity was 2,700 cc., and with the left side of the thoracic wall supported, 3,100 cc. The improvement in the vital capacity and the relative decrease in the paradoxical breathing during the last examination are in part due to the regeneration of some of the resected ribs (fig. 4 *A* and *B*).

Case 5.—The patient had undergone four operations for empyema. Three inches (7.6 cm.) of the eighth rib was removed, and the ninth, tenth and eleventh ribs were removed from the transverse processes of the vertebrae to the cartilaginous junctions. There was a funnel-shaped depression in the posterior axillary region

25. Bruns, O.: Folgezustände des einseitigen Pneumothorax. Beitr. z. Klin. d. Tuberk. **12**:1, 1909.

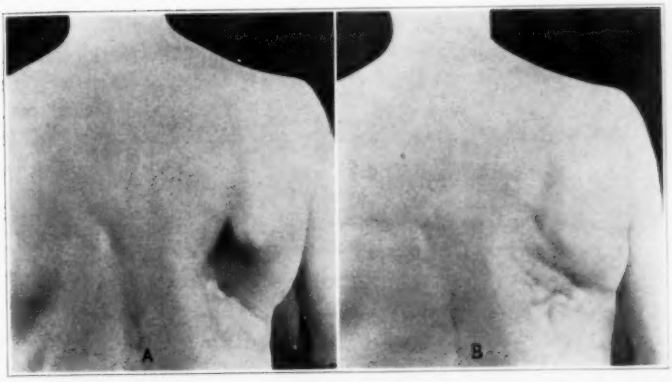

Fig. 5 (case 5).—*A*, inspiration. Note the contraction of the chest both in the region of the scar and in the lower axilla. *B*, expiration. The left side of the chest is ballooned out posteriorly; the concavity in the lateral aspect of the chest is also obliterated.

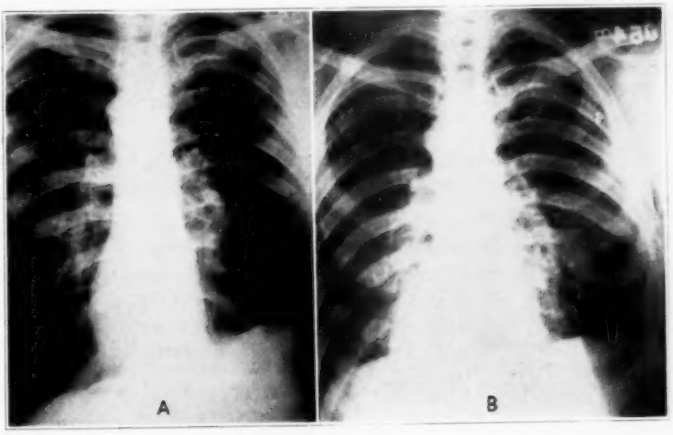

Fig. 6 (case 5).—*A*, inspiration. *B*, expiration. Note the inflation of the base of the left lung behind the liver, in the region of the resected ribs.

of the chest which was deeper on inspiration and very shallow on expiration (fig. 5 *A* and *B*). On auscultation, paradoxical breath sounds were heard over this portion of the chest; the inspirations were short and the expirations long and of tubular quality (fig. 6 *A* and *B*).

Paradoxical breathing occurs in other congenital and acquired defects in the chest wall. It has been described in fissures of the sternum,[26] in rickets,[27] in fractures of the ribs[28] and in paralysis of the intercostal nerves and of the nerves to the scalene muscles.[29]

SUMMARY

1. Paradoxical breathing occurs in all air-breathing vertebrates. It depends on the narrowing or closing of the glottis during certain respiratory acts and on the unequal pressure conditions prevailing in the different portions of the respiratory tract.

2. In the amphibians and birds, paradoxical breathing, like the maintenance of residual air, serves a useful function in moistening and diluting the atmospheric air. In mammals, owing to the oxygenation of the blood in all portions of their lungs, paradoxical breathing impairs the respiratory function by diminishing the vital capacity and by causing breathing of stale air.

3. With an intact thoracic wall, the paradoxical breathing is limited to the apical and mediastinal portions of the lungs, these regions of the chest being poorly provided with muscle. In congenital and acquired defects of the chest wall, the vicarious breathing is conspicuous in the areas of the lungs adjacent to the defects.

4. During the activities of workers such as glass blowers, singers, dancers and runners, the paradoxical breathing produces acute emphysema (volumen pulmonum acutum) and materially curtails the efficiency of the performers.

5. Paradoxical breathing is an important factor in the development of pulmonary emphysema and is largely responsible for the dyspnea and cyanosis observed in emphysema and asthma.

6. Paradoxical breathing, by causing an interchange of material between the lungs, is a common cause of the interbronchial spread of infection in tuberculosis and all other diseases of the lungs.

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26. Virchow and Senator: Case of Fissure of Sternum, Verhandl. d. Berl. med. Gesellsch. **1**:83, 1900.

27. St. Engel: Der Rachitistod, Fortschr. d. med. **40**:543, 1922.

28. Sauerbruch, E. F.: Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1925, vol. 1, p. 118.

29. Hoover, C. F.: Significance of the Respiratory Movements of the Costal Margins, Am. J. M. Sc. **159**:633, 1920.

EPINEPHRINE

ITS EFFECT ON THE CARDIAC MECHANISM IN EXPERIMENTAL HYPERTHYROIDISM AND HYPOTHYROIDISM

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Auricular fibrillation is the most frequent cardiac arrhythmia in hyperthyroidism, and in the paroxysmal form presents itself in varying degrees of frequency and duration. It usually disappears permanently when the hyperthyroidism is relieved.[1] In the patients with hyperthyroidism who have auricular fibrillation, although the state of the hyperthyroidism ostensibly may remain unchanged, the auricular fibrillation often is transitory. It seems that there may be some labile factor in these patients which in the presence of the hyperthyroid condition affects the heart so as to favor the production of the transient abnormal rhythm.

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This study was conducted in part under a grant from the Proctor Fund for the Study of Chronic Diseases.

1. Levine, S. A.: Unrecognized Hyperthyroidism Masked as Heart Disease, Ann. Int. Med. **4**:67, 1930. Levine, S. A., and Sturgis, C. C.: Hyperthyroidism Masked as Heart Disease, Boston M. & S. J. **190**:233, 1924. Willius, F. A., and Boothby, W. M.: Behavior of the Heart in Exophthalmic Goiter and in Adenomatous Goiter with Hyperthyroidism, Tr. A. Am. Physicians **38**:137, 1923. Hamilton, B. E.: Heart in Toxic Thyroid States, S. Clin. North America **4**:1411, 1924. Andrus, E. C.: Heart Failure with Hyperthyroidism, New York State J. Med. **29**:661, 1929. Lahey, F. H., and Hamilton, B. E.: Thyrocardiacs: Their Diagnostic Difficulties, Surg., Gynec. & Obst. **39**:10, 1924. Hamilton, B. E.: Clinical Notes on Hearts in Hyperthyroidism, Boston M. & S. J. **186**:216, 1922. Hurxthal, L. M.: Auricular Fibrillation in Patients with Goiter, Am. J. M. Sc. **179**:507, 1930. Dunhill, T. P.; Fraser, F. R., and Stott, A. W.: Auricular Fibrillation in Thyrotoxic Conditions, Quart. J. Med. **17**:326, 1924. Phillips, J., and Anderson, J. P.: Cardiac Disturbances in Goiter, J. A. M. A. **89**:1380 (Oct. 22) 1927. Anderson, J. P.: Auricular Fibrillation Associated with Hyperthyroidism, Am. J. M. Sc. **173**:788, 1927.

Auricular fibrillation may follow the administration of thyroid substances in man.[2] This is not of frequent occurrence, however, and the explanation of the mechanism of auricular fibrillation in hyperthyroidism probably is not to be found only in fluctuations in the thyroxine content of the tissues, since this substance is regarded as being too stable to account for such a transitory effect.[3]

Aub and Stern[4] reported a case of complete auriculoventricular heart block in which the administration of sufficient desiccated thyroid gland to raise the basal metabolic rate to 47 per cent above the normal level increased the auricular rate to 120 per minute without affecting the slow ventricular rate. It may be inferred from this that the auricles are more readily affected than the ventricles by the administration of thyroid substance.

There is other evidence that hyperthyroidism may predispose the auricles to unusually increased activity without being able in itself, perhaps, to initiate an abnormal rhythm. Yater[5] demonstrated that the perfused hearts of thyroxinized rabbits beat at a much faster rate than did the hearts of normal controls. Priestley and his associates[6] showed that the heart of one dog transplanted into the neck of another dog beat more rapidly following the administration of thyroxine to the latter. Lewis and McEachern[7] demonstrated that both the isolated hearts and the auricles of thyroid-treated rabbits continued to beat more rapidly than similar preparations from normal animals. Furthermore, isolated hearts and auricles from thyroxinized or thyroid-fed rabbits responded to epinephrine with greater absolute increases in rate and amplitude than did those of normal controls. The results of the work of Lütolf[8] are in agreement with this.

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2. Wedd, A. M.: Auricular Fibrillation Produced by Thyroid Medication, Clifton M. Bull. **17**:57, 1931. Gram, H. C.: Perpetual Arrhythmia After Use of Thyroidine, Hospitalstid. **72**:381, 1929. Hyman, H. T.: Electrocardiographic Record of a Paroxysmal Cardiac Irregularity as a Manifestation of Thyroid Administration, Am. Heart J. **5**:383, 1930.

3. Kendall, E. C.: Thyroxine, Am. Chem. Soc. Monog. Ser. no. 47, New York, The Chemical Catalog Company, 1929, chap. 21.

4. Aub, J. C., and Stern, N. S.: The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, Arch. Int. Med. **21**:130 (Jan.) 1918.

5. Yater, W. M.: Thyroxin Tachycardia in Perfused Hearts of Thyroxinized Rabbits, Am. J. Physiol. **98**:338, 1931.

6. Priestley, J. T.; Markowitz, J., and Mann, F. C.: The Tachycardia of Experimental Hyperthyroidism, Am. J. Physiol. **98**:357, 1931.

7. Lewis, J. K., and McEachern, D.: Persistence of an Accelerated Rate in Isolated Hearts and Isolated Auricles of Thyrotoxic Rabbits, Bull. Johns Hopkins Hosp. **48**:228, 1931.

8. Lütolf, W.: Investigations on the Enhancement of the Action of Adrenalin on the Surviving Mammalian Heart by Means of Thyroxin, Ztschr. f. Biol. **90**:334, 1930.

Cardiac hypertrophy in experimental hyperthyroidism has been reported by numerous writers.[9] A difference of opinion exists as to whether or not there are any histologic changes in the heart following the production of hyperthyroidsm in animals. Farrant,[10] Hashimoto,[11] Goodpasture[12] and Takane[13] reported various microscopic pathologic changes in the heart muscle in experimental hyperthyroidism. Cameron and Carmichael,[9f] on the other hand, found no histologic abnormalities in the hearts of animals with hyperthyroidism. Rake and McEachern,[14] in a carefully controlled study, reported that in the absence of infection the hearts of guinea-pigs and rabbits with hyperthyroidism showed no significant microscopic changes. The same authors studied the hearts of 27 patients dying of hyperthyroidism,[15] compared with 150 "suitable" controls, and concluded that there were no consistent significant histologic changes.

The reports of Lewis and McEachern[7] and Lütolf[8] indicate that there is an increased reaction of the hearts of animals with hyperthyroidism to epinephrine. Schermann[16] demonstrated, moreover, that hearts isolated from normal rabbits were fifty times more susceptible to the action of epinephrine than hearts isolated from thyroidectomized

9. (*a*) Iscovesco, H.: The Physiological Activity of a Thyroid Extract, Compt. rend. Soc. de biol. **75**:361, 1913. (*b*) Hoskins, E. R.: Growth of the Body and Organs of the Albino Rat as Affected by Feeding Various Ductless Glands, J. Exper. Zool. **21**:295, 1916. (*c*) Herring, P. T.: Action of Thyroid upon the Growth of the Body and Organs of the White Rat, Quart. J. Exper. Physiol. **11**:231, 1917. (*d*) Hewitt, J. A.: Effect of Administration of Small Amounts of Thyroid Gland on the Size and Weight of Certain Organs in the Male White Rat, Quart. J. Exper. Physiol. **12**:347, 1918-1920. (*e*) Cameron, A. T., and Carmichael, J.: Effect of Thyroxine on the Growth in White Rats and in Rabbits, J. Biol. Chem. **46**:35, 1921; (*f*) Comparative Effects of Thyroid and of Iodid Feeding on Growth in White Rats and Rabbits, J. Physiol. **54**:lxxiv, 1920-1921. (*g*) Simonds, J. P., and Brandes, W. W.: Size of the Heart in Experimental Hyperthyroidism, Arch. Int. Med. **45**:503 (April) 1930.

10. Farrant, R.: Hyperthyroidism: Its Experimental Production in Animals, Brit. M. J. **2**:1363, 1913.

11. Hashimoto, H.: Heart in Experimental Hyperthyroidism, Endocrinology **5**:579, 1921.

12. Goodpasture, E. W.: Influence of Thyroid Products on the Production of Myocardial Necrosis, J. Exper. Med. **34**:407, 1921.

13. Takane, K.: Experimental Acute Myocarditis Following Thyroidine and Iodin Salts, Virchows Arch. f. path. Anat. **259**:736, 1926.

14. Rake, G., and McEachern, D.: Experimental Hyperthyroidism and Its Effect upon the Myocardium in Guinea Pigs and Rabbits, J. Exper. Med. **54**:23, 1931.

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16. Schermann, S. J.: Reaction of Isolated Hearts of Thyroidectomized Animals to Adrenalin, Arch. f. exper. Path. u. Pharmacol. **126**:10, 1927.

animals. Andrus [17] showed that following the administration of epinephrine intravenously there is a definite increase in the rate of intra-auricular conduction time in normal cats and dogs. This occurred with doses of from 0.25 to 1 cc. of a 1 : 50,000 solution. Allen found that the injection of even larger doses of epinephrine than these caused no arrhythmias in normal rabbits and dogs.[18]

Cowan, however, stated that auricular fibrillation may be produced by the injection of epinephrine into laboratory animals in either the intact state [19] or in a heart perfusion preparation.[20] Otto [21] wrote that "practically every known type of arrhythmia," including auricular fibrillation, may occur in normal animals following the injection of epinephrine. Neither of these authors quoted any experimental evidence in support of these statements.

Premature auricular and ventricular beats and complete dissociation of the auricles and ventricles were reported following the injection of epinephrine into normal animals [22] and man.[23] Ventricular fibrillation following the injection of epinephrine into normal cats under chloroform anesthesia was reported by Levy.[24]

Four cases have been reported [25] in which transient auricular fibrillation occurred in patients following the injection of epinephrine. In one of these patients [21] spontaneous auricular fibrillation had appeared

17. Andrus, E. C.: Action of the Sympathetic upon the Excitatory Process in the Mammalian Heart, J. Exper. Med. **45**:1017, 1927.

18. Allen, W. F.: Bigeminal Pulse in Rabbits, Am. J. Physiol. **95**:190, 1930.

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23. (*a*) Danielopolu, D., and Danulesco, V.: Paroxysmal Ectopic Tachycardia in Man Produced by Adrenalin, Ann. de méd. **10**:1, 1921. (*b*) Clough, H. D.: Effect of Epinephrine on Electrocardiogram of Patients with Irritable Hearts, Arch. Int. Med. **24**:284, 1919. (*c*) DeGraff, A., and Weiss, S.: Observations on the Extrinsic Nervous Control of the Auricles and Ventricles in Complete A-V Block in Man, J. Clin. Investigation **2**:227, 1926. (*d*) Otto, H. L., and Gold, H.: Persistent Premature Contractions, Arch. Int. Med. **38**:186 (Aug.) 1926. (*e*) Hume, W. E.: The Action of Adrenalin Chloride on the Human Heart, Quart. J. Med. **21**:459, 1928.

24. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals under Chloroform Anesthesia, Heart **4**:319, 1912-1913.

25. (*a*) Smith, F. M., and Moody, W. B.: Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, Arch. Int. Med. **32**:192 (Aug.) 1923. (*b*) Otto.[21] (*c*) Hume.[23e]

previously, and in another [25a] auricular fibrillation previously had followed forced deep breathing. In none of these four cases was specific evidence for or against hyperthyroidism mentioned. Tompkins, Sturgis and Wearn [26] injected 0.5 cc. of a 1 : 1,000 solution of epinephrine into three patients with hyperthyroidism according to the method of Goetsch.[27] The authors followed the changes in blood pressure and pulse rate, but did not mention the presence or absence of arrhythmia.

As hyperthyroidism increases the activity of the heart, especially that of the auricles, and has been shown to enhance the cardiac response to epinephrine, it was decided to try the effect of epinephrine on the rhythm of the intact hearts of normal animals and of those with hyperthyroidism and hypothyroidism.

METHOD OF EXPERIMENTATION

A Benedict portable respiration machine [28] was used to determine the oxygen consumption of the rabbits. It had an outside electric blower and was attached to a water-sealed animal chamber. The apparatus was tested twice weekly to demonstrate the absence of leaks. Wilson's soda lime was used for carbon dioxide absorption. A water vapor absorbent was not used.

The rabbits were kept on a diet of oats, alfalfa hay and lettuce. Their average weight was 2,400 Gm. They were made to fast from sixteen to eighteen hours before each determination of metabolism. The oxygen consumption was noted for successive ten minute periods until three or four consecutive checks were obtained. The temperature readings of the oxygen reservoir were recorded every ten minutes, and the barometric pressure was read at the beginning of each determination. The determinations of the basal metabolic rate on normal animals agreed with the results of other experimenters.[29]

Seventeen rabbits were used and were divided into three groups. Hyperthyroidism was produced in the first group of ten animals. Four were given desiccated thyroid gland, 0.260 Gm. (4 grains) daily by mouth. In three others hyperthyroidism was induced in a similar way. Then thyroid feeding was discontinued until the basal metabolic rate became normal. It was then resumed until a second state of hyperthyroidism was obtained. The remaining two animals were given thyroxine, 0.001 Gm. ($\frac{1}{60}$ grain) daily subcutaneously for three days. The second group consisted of three rabbits; they were thyroidectomized, and their basal metabolic rates were followed until a definite hypothyroidism developed.

26. Tompkins, E. H.; Sturgis, C. C., and Wearn, J. T.: The Effects of Epinephrine on the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Men, Arch. Int. Med. **24**:269 (Sept.) 1919.

27. Goetsch, E.: Diagnosis of Thyroid Disorders, New York State J. Med. **18**:259, 1918.

28. Benedict, F. G.: A Portable Respiration Apparatus for Clinical Use, Boston M. & S. J. **178**:667, 1918.

29. Krogh, A.: Respiratory Exchange in Animals and Man, New York, Longmans, Green & Co., 1916, p. 141. Webster, B.; Clawson, T. A., and Chesney, A. M.: Heat Production in Goitrous and Non-Goitrous Animals, Bull. Johns Hopkins Hosp. **43**:278, 1928. Lund, C. C., and Benedict, E. B.: Influence of the Thyroid Gland on the Action of Morphine, New England J. Med. **201**:345, 1929.

Autopsy was performed on one five months after operation, and gross findings in agreement with those reported by Tatum[30] in myxedematous rabbits were found. The third group was composed of five normal rabbits which were used as controls.

Epinephrine was injected intravenously into each animal of these groups. Electrocardiograms were taken immediately before, during and after the injections and until all the effects produced by the injection had disappeared permanently. Any changes that occurred disappeared permanently within from ten to fifteen minutes after the injection. In three of the animals of the first group, injections and tracings were made during the first period of hyperthyroidism; in the ensuing normal state and in the second period of hyperthyroidism.

Forty-five experiments were made on these seventeen rabbits. The amounts of epinephrine injected varied from 0.5 cc. of 1:1,000 to 1 cc. of 1:1,000,000 dilutions. Epinephrine was not administered on the basis of a given amount per kilogram of body weight, because of the close similarity of the weights of the animals to the average weight of the group (2,400 Gm.). The differences in weight that did exist did not seem to play a part in the reactions of the animals. Orientation

Effect on the Cardiac Rhythm of the Injection of Epinephrine into Normal Rabbits and into Those with Hyperthyroidism and Hypothyroidism *

No. Animals	No. Experiments	Average BMR, per Cent	Dilutions of Epinephrine	Dose, Cc.	PVT	AF	ES	Ch. Q-R-S	NR	Slw	VF	Death
5	20	+75	1:100,000	1.0	20	5	2	1	7	..	..	..
3	3	−34	1:100,000	1.0	..	..	..	..	..	3	..	..
6	6	± 0	1:100,000	1.0	..	..	..	..	..	6	..	..
4	5	+82	1:1,000	0.1 to 0.5	3	2	..	1	..	..	3	3
4	4	± 0	1:1,000	0.1 to 0.5	3	..	2	1	1	1	1	1

* Abbreviations in the table represent the following: BMR, basal metabolic rate (per cent of normal); PVT, paroxysmal ventricular tachycardia; AF, auricular fibrillation; ES, extrasystoles; Ch. Q-R-S, changing form of Q-R-S complex; NR, nodal rhythm; Slw, slowing of the rate; VF, ventricular fibrillation.

Note the frequency of auricular fibrillation in the animals with hyperthyroidism and its absence in the normal animals and those with hypothyroidism.

experiments showed that the dose most suitable to compare the reactions of normal animals and of those with hyperthyroidism and hypothyroidism was 1 cc. of 1:100,000 dilution of epinephrine (0.01 mg.). Doses smaller than this did not produce consistent electrocardiographic changes. Solutions of epinephrine hydrochloride were made by diluting epinephrine (1:1,000) with Ringer's solution. This diluent when injected alone produced no changes in the electrocardiogram.

RESULTS

Twenty injections of 1 cc. of 1:100,000 epinephrine made into five rabbits with hyperthyroidism produced the following electrocardiographic effects: paroxysmal ventricular tachycardia, nodal rhythm, probable auricular fibrillation and ectopic beats (table). Each injection of this dose of epinephrine was followed promptly by a paroxysm of ventricular tachycardia (fig. 1 *A*). Transient auricular fibrillation (fig. 1 *B*) occurred after four injections, appearing immediately or within a half-minute after the ventricular tachycardia had disappeared.

30. Tatum, A. L.: Morphological Studies in Experimental Cretinism, J. Exper. Med. **17**:636, 1913.

In three other instances, changes consistent with auricular fibrillation, although not quite as definite as those mentioned, were noted (fig. 1 *C*). The electrocardiographic changes that were interpreted as indicative of auricular fibrillation were: (1) grossly irregular ventricular rhythm, (2) absence of the auricular (P) waves and (3) the presence of fibril-

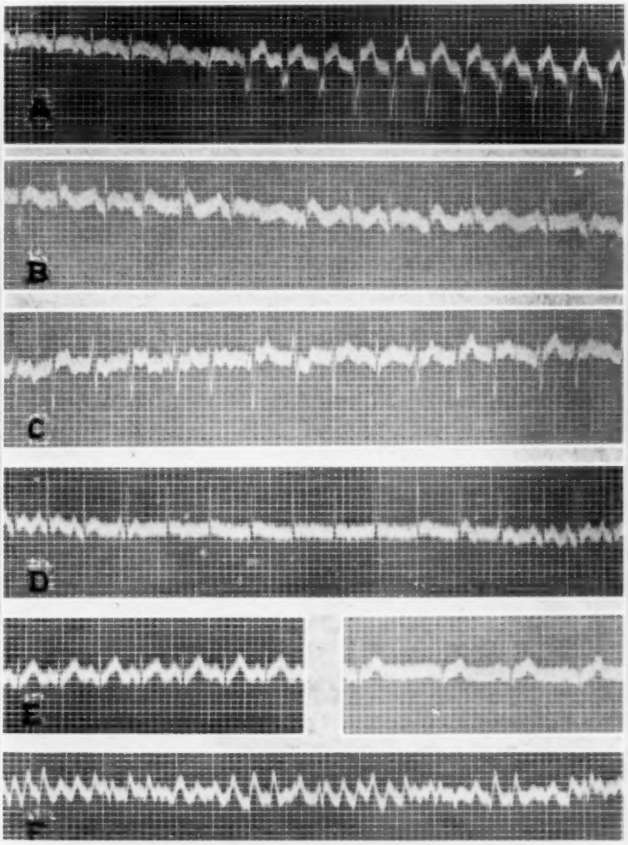

Fig. 1.—*A* shows development of a characteristic attack of paroxysmal ventricular tachycardia in a rabbit with hyperthyroidism following 1 cc. of 1:100,000 epinephrine intravenously. *B* shows auricular fibrillation produced by 1 cc. of 1:100,000 epinephrine in a rabbit with hyperthyroidism. *C* is similar to *B*, except that the curves are suggestive of auricular fibrillation. *D*, same as *A*, except the mechanism here is nodal rhythm alternating with normal rhythm. *E* shows the slowing following 1 cc. of 1:100,000 epinephrine in a normal rabbit or one with hypothyroidism. *F* shows ventricular fibrillation following a large dose of epinephrine (0.25 cc. of 1:1,000) in a rabbit with hyperthyroidism.

lary (ff) waves. In two animals (in one of which an irregularity corresponding to the foregoing criteria of auricular fibrillation had twice developed) the injections of epinephrine (1 cc. of 1:100,000) were followed in the usual way by paroxysmal ventricular tachycardia, but after this the electrocardiogram showed a slow, regular ventricular action and absence of the auricular (P) waves. We have interpreted this as auriculoventricular nodal rhythm (fig. 1 *D*); it occurred seven times in these two rabbits with hyperthyroidism.

The dose (1 cc. of 1:100,000) given to three normal rabbits, three rabbits with hypothyroidism and three rabbits which previously had had hyperthyroidism but now had a normal basal metabolic rate was followed in each case by only a transient slowing of the rate without irregularity (fig. 1 *E*). This appeared within a few seconds after the injection and continued for about one to one and a half minutes. The rate then returned to normal (table).

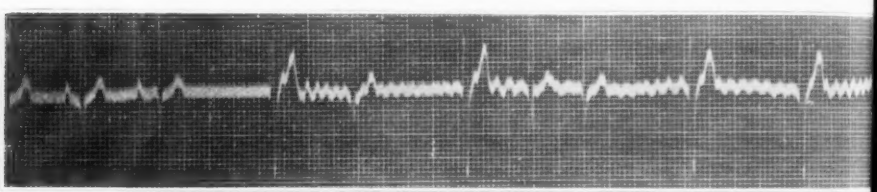

Fig. 2.—The development of auricular fibrillation in a dog with hyperthyroidism about forty-five seconds after the intravenous injection of 0.5 cc. of 1:10,000 epinephrine.

Larger doses of epinephrine were given to both normal rabbits and those with hyperthyroidism. Five injections (with from 0.1 to 0.5 cc. of 1:1,000 dilution) were given to four rabbits with hyperthyroidism. In three of the animals ventricular tachycardia developed immediately after the injections. This was followed by ventricular fibrillation (fig. 1 *F*) and death. The fourth animal did not die and injection was made twice. Following one injection in this rabbit only changing Q-R-S complexes developed, and after the second injection, several days later, transient auricular fibrillation occurred (table). Similarly large doses (from 0.1 to 0.5 cc. of 1:1,000) were given also to four normal rabbits. In three paroxysmal ventricular tachycardia developed promptly; in the fourth numerous ectopic ventricular beats, but no tachycardia. The latter animal, however, received the smallest dose (0.1 cc). All these rabbits recovered, except one in which ventricular fibrillation developed. This animal was given the largest dose (0.5 cc., table).

COMMENT

The frequent but by no means constant coexistence of transient auricular fibrillation and hyperthyroidism clinically led us to suspect that some factor in addition to the hyperthyroidism might be responsible for the cardiac arrhythmia. It is obvious that the heart structure must be the same at the moment auricular fibrillation develops as it was the moment before when the heart was beating regularly. One can readily picture a sudden change in the functional or nervous properties of the heart which could produce alterations in rhythm. The clinical observation that in some patients with hyperthyroidism paroxysms of auricular fibrillation develop immediately following a sudden emotional strain suggested the possibility that the suprarenals may be playing a rôle in the production of auricular fibrillation when hyperthyroidism is present. Furthermore, from experimental data it was shown that the cardiac response to epinephrine is greater in the presence of hyperthyroidism.[7, 8] Therefore it was decided to study the effect of epinephrine on the cardiac rhythm in animals with hyperthyroidism and to control these experiments by observations on normal animals as well as on those with hypothyroidism. The experiments indicate that the smallest doses of epinephrine which are followed by various cardiac arrhythmias in animals with hyperthyroidism produce no change in the cardiac rhythm of normal animals. Doses of epinephrine large enough to cause significant arrhythmias consistently in normal animals usually caused death when given to animals with hyperthyroidism. Paroxysmal ventricular tachycardia was the most frequent arrhythmia following the injection of epinephrine into normal animals or those with hyperthyroidism, provided enough epinephrine was given to produce any significant change. Electrocardiographic changes consistent with auricular fibrillation occurred after seven of the twenty-five injections (28 per cent) into rabbits with hyperthyroidism.

It is interesting to compare the results of injections of epinephrine in some of the rabbits of group 1 during the hyperthyroid, the ensuing normal and the second hyperthyroid states. In the hyperthyroid state these animals exhibited a marked cardiac response to small doses of epinephrine, as evidenced by paroxysmal ventricular tachycardia, extrasystoles, auricular fibrillation and nodal rhythm. After the basal metabolic rate had dropped to normal, they reacted to the same dose of epinephrine with slowing of the rate only, just as the three normal rabbits and the three with hypothyroidism reacted. This demonstrates the transient effect of experimental hyperthyroidism on the hearts of this group of animals as evidenced by the reaction to epinephrine. When hyperthyroidism was again developed, their response to epinephrine was similar to that in the first experiment.

Injections of epinephrine in increasing amounts were given to normal rabbits until a lethal dose was administered, but tracings indicative of auricular fibrillation never were obtained in this group. The dose of epinephrine necessary to kill a normal rabbit apparently was from two to five times greater than that required for a lethal result in rabbits with hyperthyroidism. Petzetakis[31] reported the occurrence of auricular fibrillation following lethal doses of epinephrine to normal rabbits. The amounts that he gave varied from 1 to 1.5 mg. per kilogram of body weight. These doses were about six to seven times greater per kilogram than the largest lethal dose used in our experiments. In his experiments sublethal doses given to normal animals did not cause auricular fibrillation.

The difficulty of interpreting electrocardiograms of rabbits is well recognized because of the small size of the complexes and the normally rapid rate, which is increased in hyperthyroidism. It is possible that an animal which has a heart larger than that of a rabbit would be preferable for the study of cardiac arrhythmias. Accordingly, trial experiments were made on two large dogs. Each weighed 22 Kg. One was fed from 10 to 15 Gm. of desiccated thyroid gland daily for three weeks, and the other was given 10 mg. of thyroxine subcutaneously daily for three days. Following this, electrocardiographic tracings were taken before, during and after the giving of varying amounts of epinephrine. All injections of epinephrine were given intravenously.

It was found that the largest dose of epinephrine which would not cause arrhythmia in these dogs when they were normal was 0.5 of 1 : 1,000. After hyperthyroidism was produced, however, the same dose consistently produced premature ventricular beats and questionable sino-auricular block in both dogs. In the second dog on one occasion auricular fibrillation was produced by this dose (fig. 2). The state of the hyperthyroidism was evidenced by tachycardia, slight diarrhea and moderate loss of weight. The basal metabolic rates were not determined. When thyroxine was used to induce hyperthyroidism, the injections of epinephrine were made on the second, third and fourth days after the last administration of thyroxine. The administration of thyroid was discontinued for two months in both dogs. Then each was given 5 mg. of thyroxine subcutaneously daily for three days, and injections of epinephrine were made in the same way as described previously. This time no auricular fibrillation was noted; otherwise the cardiac reactions of the dogs, according to the electrocardiographic tracings, were the same as when they had hyperthyroidism for the first time.

31. Petzetakis, M.: Electrocardiographic Study of the Action of Adrenalin on the Cardiac Rhythm of the Rabbit, J. de physiol. et de path. gén. **29**:428, 1931.

CONCLUSIONS

1. The effect of epinephrine on the cardiac mechanism in normal rabbits and in those with hyperthyroidism and hypothyroidism was studied with the electrocardiograph.

2. The hearts of rabbits with hyperthyroidism were more susceptible to the action of epinephrine than were the hearts of normal animals and those with hypothyroidism.

3. Auricular fibrillation was produced in rabbits with hyperthyroidism and in one dog with hyperthyroidism by amounts of epinephrine insufficient to affect the cardiac rhythm of these animals when they did not have hyperthyroidism.

4. Paroxysmal ventricular tachycardia was produced in rabbits with hyperthyroidism by doses of epinephrine too small to alter the normal cardiac rhythm of normal animals or those with hypothyroidism.

5. The minimal lethal dose of epinephrine in rabbits was diminished in the hyperthyroid state.

SYNDROME OF PNEUMOCOCCIC BRONCHIAL OBSTRUCTION

EXPERIMENTAL PRODUCTION OF ATELECTASIS OR LOBAR PNEUMONIA WITH HUMAN PNEUMONIC SPUTUM; SUGGESTION FOR PREVENTIVE AND THERAPEUTIC TREATMENT

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It is only within relatively recent years that the importance of bronchial obstruction for the production of a wide variety of pulmonary diseases has come to be more generally recognized. True, in frank foreign body obstruction of a bronchus, it has been known that absorption of the air and atelectasis can ensue. Aside from advancing the therapy of this type of obstruction, Chevalier Jackson was the first to recognize atelectasis as a symptom of bronchial obstruction by diphtheritic membranes and to cure so-called diphtheritic pneumonia by bronchoscopic aspiration. William Pasteur in 1890 had noticed the frequent occurrence of atelectasis ("massive collapse") of the lung in diphtheria, but ascribed it etiologically to paralysis of the diaphragm, which he thought could bring about the airless state of the lung. In Pasteur's cases the high diaphragm was the result and not the cause of the condition; for it is well known today that paralysis of the diaphragm cannot produce atelectasis.

Experimentally, it was shown by Traube in 1844 that mechanical occlusion of a bronchus by shot or gum arabic could produce atelectasis. Mendelssohn in 1846 demonstrated, in addition, that open pneumothorax could result in the same condition; in a recent paper we have explained this on the basis of the complete collapse and occlusion of bronchioli that occur following pneumothorax and the absorption of alveolar gases by the blood in the same manner as if a bronchus were completely obstructed. Lichtheim in 1879 proved beyond doubt the importance of complete bronchial obstruction and of the integrity of the pulmonary circulation for the absorption of gases and the production of

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an airless state of the lung. He was the first to demonstrate the relative speeds of absorption of carbon dioxide, oxygen and nitrogen from the lung, although his actual figures are slightly different from the more refined determinations we have recently made.

Clinically, Legendre and Bailly in 1844 noticed the frequent coincidence of atelectasis and bronchitis in children, and considered bronchial obstruction with secretions as playing a part in its causation. The true mechanism of its production was, however, little understood by these authors. Gairdner in 1851 also noticed the occurrence of atelectasis with bronchitis and ascribed it to a mechanical ball-valve bronchial obstruction by mucus on inspiration—an explanation which supposes a perfect functioning of mucus as a valve; they failed to understand, however, that even by such a process complete removal of alveolar air is impossible without the aid of the pulmonary circulation. Barthels in 1860 observed mucus obstruction of the corresponding bronchi at postmortem examination in cases of atelectasis, including those occurring in patients with diphtheria. He remarked that Virchow first called attention to the necessity of the pulmonary circulation for absorbing alveolar air after complete bronchial obstruction, and concurred in the view that mechanical expulsion of air, alone, could not satisfactorily explain the production of atelectasis. Pearson-Irvine in 1876 had already reported a case of atelectasis complicating diphtheria, thus antedating William Pasteur's reports by a few years. Along with his own cases, Pasteur later reported a case of Samuel West's, in which atelectasis "followed the obstruction of a main bronchus by a cast."

We recently performed a thoracoplasty on a white woman, 27 years old, with tuberculosis of the left lung, at the Metropolitan Hospital, New York. Twenty hours after operation typical atelectasis developed, and the patient was moribund. Under the influence of hyperventilation with oxygen and carbon dioxide, a profuse expectoration of mucus was started; and this mucus when put in water assumed the typical form of a large bronchial cast. The patient recovered. Bacteriologic examination showed the presence of pneumococci of type IV in almost pure culture.

From the foregoing paragraphs it is readily seen that the groundwork for demonstrating the rôle of bronchial obstruction in at least one phase of pulmonary disease (atelectasis) was thus laid a good many years ago. It is nevertheless probably true that the "literary bombardments" of William Pasteur, who reported a series of cases in 1890, 1908, 1910 and 1914, were a decided factor in impressing "massive collapse" (atelectasis), as an entity, on the clinical consciousness. But if this clinical recognition was becoming established, the ideas on the pathogenesis of atelectasis were becoming more and more confused, not to say fanciful, until only very recently. It seems pitiful that the papers of Traube and

Mendelssohn and the monumental work of Lichtheim should have been so completely overlooked, forgotten or ignored as to give rise to the heated controversy on the pathogenesis of "massive collapse" to which Pasteur, Rose-Bradford, Briscoe, Bergamini and Shephard, Scott and a host of others have contributed. This phase of the subject forms an interesting chapter, for the details of which the reader is referred to our other papers. In these are discussed at length the various theories of pathogenesis, paralysis of the diaphragm, "bronchomotor reflex," bronchial constriction, mechanical expulsion of air, "angioneurotic edema," "hydremic plethora," etc.—a formidable list of barriers to a true understanding of the pathogenesis and therapy of atelectasis, which, we believe, have finally been removed with the aid of sound physicochemical and physiologic principles.

According to our findings there is only one final mechanism in the production of atelectasis—complete bronchial obstruction and absorption of the gases in the alveoli by the circulating blood according to definite laws. A ball-valve obstructing mechanism may modify the speed of the production of atelectasis, but complete absorption of alveolar air and atelectasis cannot ensue without complete bronchial obstruction. The rate of production of atelectasis is dependent on the particular gases or vapors that happen to be in the lung. When bronchial obstruction is *complete* and the *pulmonary circulation normal*, atelectasis occurs; without these two factors atelectasis cannot occur. There are many contributory factors in atelectasis, such as the absence of cough, splinting of the chest, edema of the bronchial mucosa and viscid sputum; but there is only one mechanism of its production—bronchial obstruction. The truth of this contention is especially evident in postnatal atelectasis, in which the absence of aeration of the lung and the persistence of "fetal lung" can be ascribed to no other cause than bronchial or bronchiolar obstruction. The cause of this obstruction has been repeatedly found to be amniotic fluid and dermal cells (Coryllos, Henderson). It is of interest to notice here the importance of this bronchial obstruction to subsequent development of lobar pneumonia or bronchopneumonia in these new-born infants. In fact, Cruickshank in a special report of the Medical Research Council on the causes of neonatal death gave the results of 800 autopsies; in 179 of the cases the condition causing death was pneumonia, so that "the frequency of pneumonia was practically 23 per hundred deaths; many of these cases which have been placed in the group of 'death from infection' were predisposed to these infections by the effect of birth asphyxia" due to bronchial obstruction.

The mechanism of lobular or patchy atelectasis we consider as likewise dependent on complete occlusion of lobular bronchi, with this additional requisite: that absorption of air from a lobule presupposes sufficient inflammation of the parenchyma to prevent the physiologic

interchange of gases between lobules, so that the gases within a lobule can be completely absorbed. Van Allen and Adams showed that this interchange normally exists and prevents lobular atelectasis, even with complete bronchial obstruction. We do not agree with them, however, on the necessity for "alveolar pores," the gaseous exchange between alveoli through the interalveolar septums, which are normally permeable to gases, being physiologic. The same mechanism of production of lobular atelectasis obtains as for lobar atelectasis; but we cannot agree with Diaz that lobar atelectasis always starts as patchy atelectasis, because on the latter supposition we could not explain the sudden onset of the disease and its lobar distribution from the start, as shown by roentgen and physical signs. We do not deny, however, that originally patchy areas may, by confluence, simulate a lobar distribution.

In this country the first true correlation of experimental and clinical data was established by Jackson, who cured diphtheritic atelectasis by bronchoscopic aspiration of membranes (1925). Subsequently, Harrington in 1927 successfully treated a patient with postoperative atelectasis ("drowned lung") by seventeen successive bronchoscopies in which large volumes (several hundred cubic centimeters) of thin, serous exudate were aspirated from the lung. In the same year, Hearn and Clerf reported the bronchoscopic aspiration of thick, purulent mucus from the trachea and bronchi in a case of postoperative atelectasis.

In recent papers Jacobaeus and Westermark reported the occurrence of atelectasis in typical bronchial obstruction after hemorrhage in pulmonary tuberculosis, and also in obstruction of the bronchi by granulation tissue. Wilson reported massive atelectasis after pulmonary hemorrhage in pulmonary tuberculosis. Bronchial casts of clotted blood and fibrin were coughed up, and the lung was almost normal in twelve days.

Muller, Overholt and Pendergrass in a paper on postoperative pulmonary hypoventilation reported a high position of the diaphragm. The decrease of the bronchial air currents, in their opinion, is conducive to stagnation of bronchial secretions and consequent bronchial obstruction. Packard reported five nonsurgical cases of tuberculosis, with symptoms and signs of atelectasis, in which there was chronic fibrous pulmonary tuberculosis. One case was complicated by pulmonary carcinoma and one by a benign tumor of the lung. He concluded that fibrous occlusion of the bronchi or complete obstruction by bronchial glandular enlargement was the cause of the atelectasis. Jones reported two cases of atelectasis occurring without previous operation. One was in a boy of 8, who fractured his right humerus in an automobile accident. Three days later massive atelectasis of the left lung was noted. The other was in a girl, 18 months old, in whom in the course of measles a left-sided atelectasis developed.

The first successful bronchoscopic aspiration in lobar pneumonia (performed on a boy, 19 years old, at the New York Hospital) was reported by one of us (Coryllos) in July, 1929, in a paper concerning a series of nine bronchoscopic aspirations in lobar pneumonia, performed with the collaboration of Dr. L. A. Conner, Dr. Alexander Lambert and Dr. J. Kernan. Mainzer in 1931 reported two cases of lobar pneumonia with the physical and roentgen signs of atelectasis:

> The first occurred in a man, 30 years old, who three days prior to admission had had a chill. On admission, his temperature was 103 F.; his pulse rate, 120, and his respiration rate, 30. Roentgen examination showed complete right pneumonia with dextrocardia. Bronchoscopy was performed. The mucosa of the trachea and right bronchus was deep red. Three centimeters below the carina a gelatinous mass was noted in the right main bronchus which, when removed, amounted to 18 cc. Instantaneous relief of dyspnea ensued. This materal contained many pneumococci and a few streptococci and staphylococci. The same evening the temperature was 98 F. The following morning an increased pulse rate and a rise of temperature, with marked dyspnea, were noted. The next morning a second bronchoscopy was performed, with aspiration of 12 cc. of mucopus. Twelve hours after this the roentgen picture was practically normal. Thirty-six hours after the second bronchoscopy a third bronchoscopy was performed, and 6 cc. of "dirty mucoid material" was aspirated from the right main bronchus.
>
> The second case occurred in a man, 43 years old, who at the time of a fracture of the right leg was suffering from a "cold" and bronchitis. His bronchitis continued, and four weeks after the fracture his temperature rose to 103.2 F., his pulse rate to 130 and his respiration rate to 30. The x-ray picture showed "pneumonia" of the left lower lobe. Bronchoscopy was performed. Three centimeters below the carina, in the left main bronchus, a gelatinous secretion too thick to aspirate was sponged up, after which 1 ounce (29.5 cc.) of "thick mucopurulent dirty material" was aspirated from the left bronchus. This material contained many pneumococci and streptococci. Immediate relief followed, with the temperature, pulse and respiration normal by the following morning. Sixteen hours after bronchoscopy the lung was almost entirely clear.

A. L. Brown recently reported bronchoscopic observations in postoperative atelectasis and following therapeutic hyperventilation with carbon dioxide. He concluded that introduction of the bronchoscope may by itself free otherwise firmly fixed bronchial plugs. He noticed the almost complete obstruction of a main bronchus by edema of the mucosa. The effects of carbon dioxide ventilation as seen bronchoscopically were (*a*) an increased rate and depth of respiration, (*b*) violent movements of the tracheobronchial tree and alterations in the shape of the lumens of the bronchi, thereby tending to free adherent mucus, and (c) a distinct blanching of the mucous membrane of the trachea and bronchi.

Shortly after our report in 1928 of the experimental production of atelectasis, Lee, Raydin, Tucker and Pendergrass reported its experimental production in the dog by the instillation into a bronchus of mucus aspirated bronchoscopically from a patient with postoperative

atelectasis. The animal was previously heavily morphinized and subjected to abdominal incision and tight bandaging of the upper part of the abdomen in order to simulate postoperative conditions. In the same year we demonstrated the experimental and clinical similarities and relations of postoperative atelectasis, postoperative pneumonia and lobar pneumonia; lobar pneumonia was considered as a "pneumococcic atelectasis"—that is, an accident occurring in the course of pneumococcic bronchitis and occasioned by complete lobar bronchial obstruction by mucus or exudate infected with virulent pneumococci. Postoperative atelectasis and postoperative pneumonia were considered as arising in the same manner, but with an occluding exudate infected with less virulent pneumococci. The correctness of this hypothesis was supported by the bronchoscopic observations which one of us (Coryllos) carried out in nine cases of lobar pneumonia in which the bronchus to the affected lobes in each case was invariably found occluded with viscid exudate, which was aspirated. In a subsequent paper (1930) Coryllos developed this concept in relation to postoperative pulmonary complications.

In 1918 Allen O. Whipple demonstrated the presence of pneumococci of low virulence in the sputum of patients with or without preoperative bronchitis. If postoperative pneumonia developed, the same organism was obtained. He expressed the belief that this type of postoperative pneumonia is identical with the mild medical type of lobar pneumonia called "maladie de Woillez" (1848), described by Carrière, in which the affected lobe is airless and beefy to feel, and its alveoli are filled with reddish fluid exudate. These are indeed the characteristics of the lung in postoperative atelectasis, mild postoperative pneumonia and early red hepatization in lobar pneumonia.

The importance of a previous "cold" and bronchitis as factors conducive to postoperative atelectasis, postoperative pneumonia and lobar pneumonia is well known. This is explicable in the light of the work of Dochez, Shibley, Mills and Kneeland, who demonstrated the tremendous increase of pneumococci in the throats of monkeys after they had been given a common infectious cold. Healthy monkeys seldom showed pneumococci in their mouths and then only in small numbers. The part played by a "cold" in preparing the "soil" for growth of pneumococci thus seems apparent. In the sputum of acute bronchitis, postoperative atelectasis, postoperative pneumonia and lobar pneumonia, pneumococci are invariably found; and these organisms are the particular ones associated with the production of an exudate viscid enough to cause obstruction of a lobar bronchus. Ninety-five per cent of cases of lobar pneumonia are associated with pneumococci, the other 5 per cent being associated with Friedländer's bacillus, which is also outstanding for the viscid type of exudate that it produces. Wadsworth showed that gener-

ally the more virulent the microbe, the more fibrinous the exudate is; and this could explain the variable duration of the bronchial obstruction and the toxicity of lobar pneumonia, depending on the virulence of the pneumococcus concerned.

Viewed from this angle, the pathogenesis of postoperative atelectasis (lobar or lobular) and postoperative pneumonia (lobar or lobular) becomes clear, and their close relation becomes evident. Furthermore, these considerations give one a clue to the mechanism of the production of the medical forms of the same diseases—that is, without operation—designated by the names lobar pneumonia and bronchopneumonia, and explain in a simple and clear way a number of peculiarities of these diseases which have so far seemed inexplicable. Take, for example, the case of atelectasis with a considerable volume of mucoid sputum in the trachea and along the walls of the right or left main bronchus, and even into the mouth of the bronchus to the affected lobe. This set of conditions is sufficient under the circumstances to produce atelectasis in a case in which breathing is painful, in which narcosis, morphine or feebleness of the patient has eliminated or reduced the effectiveness of the cough reflex, and in which the patient's position on the "bad" side favors mucus stagnation. Improvement and beginning re-aeration of the lung may occur by spontaneous recovery of an effective cough; or by turning the patient on his "good" side—when a type of internal drainage of the mucus with overflow into the other main bronchus can occur, with a sudden cyanosis and strong spell of coughing, which may bring up large masses or lumps of mucoid material. Often this greatly relieves or cures the patient's dyspnea and cyanosis, and the subjective symptoms leave (L. Sante). As early as 1890 Pasteur tried this treatment combined with artificial respiration. Immediately after such a spell, the lobe will have started re-aeration, a fact easily proved by roentgenograms. When this occurs within a few hours to a day, it would indicate an obstruction relatively limited to a large bronchus. At any rate, complete removal of mucus or exudate along the length of a bronchial airway is not a sine qua non for re-aeration of the corresponding lung tissue—it is only necessary that on inspiration air be drawn into the airways by passing between the obstructing mass and the bronchial wall and by this means gradually getting below smaller or larger columns of mucus in a bronchus. The greater the re-aeration, the more effective does cough become. For patchy atelectasis the same mechanism must obtain, the disseminated obstructed lobules becoming gradually but not simultaneously aerated, so that the signs of therapeutic or spontaneous relief are more gradual and not so dramatic as in the lobar type of the disease.

If postoperative pain, splinting of the abdomen and chest, lying on the affected side, morphinization and inhibition of the cough reflex

should continue, the stage is set against re-aeration of a lobe or lung. Pneumococci already harbored in the bronchial secretions travel downward into the lymphatics and the finer bronchioles and alveoli with the inevitable outpouring of serum, fibrin and leukocytes. If the virulence of the microbes is moderately high, a more or less toxic state of the patient ensues, and the diagnosis between atelectasis and pneumonia becomes more difficult.[1] Re-aeration of the lung is more difficult, owing to the rapid, shallow breathing, the feebleness of the patient and the occlusion of the finer bronchioles and filling of the alveoli with a variable fibrinous exudate. Should one be dealing with a pneumococcus of high virulence, this mechanism needs only to be extended a step further to give the complete clinical and pathologic picture of lobar pneumonia.

We have described the *contributory factors* which in postoperative atelectasis and postoperative pneumonia are conducive to bronchial occlusion by even a relatively thin exudate—pain, posture, splinting of the abdomen and chest, and inhibition of cough by the anesthetic, narcotics or voluntary effort. This is illustrated by the cases of "drowned lung," such as the one mentioned, in which Harrington performed seventeen bronchoscopic aspirations of large volumes of thin serous fluid. In the cases in which no operation is performed—that is, in which medical lobar pneumonia ensues—these contributory factors will usually not have been in play. The possibility of physiologic damage to the cilia of the bronchial epithelium or of a decreased sensibility of the mucosal cough reflex which follows a preceding bronchitis must be admitted. Nevertheless, cough—the "watch-dog" of the lung—and bronchitis have usually been present. In spite of the preceding cough, a dramatic onset with chills and fever ushers in the acute catastrophe—a pneumococcic bronchial obstruction which is an accident in the course of a pneumococcic bronchitis. When this happens, we are apt to forget or to overlook the fact that the "makings" of the drama have previously been at hand, and we say that there have been no premonitory symptoms. Aside from preliminary bronchitis, the patient has been well. The inquiring mind will ask how it is that lobar pneumonia is not more

1. It is too early as yet to judge the therapeutic value of artificial pneumothorax, which Coghlan recently applied in six cases of lobar pneumonia. Marked clinical relief and therapeutic value are claimed by this author using this procedure. Similar clinical relief and therapeutic value have been reported for pneumothorax in postoperative atelectasis by Farris, Elkin and Habliston. Without discussing here the theoretical merits or the objections to pneumothorax, we wish to point out that the symptomatic relief reported as obtained by its use appears to be further evidence of the close relationship existing between postoperative atelectasis and lobar pneumonia (lobar pneumococcic atelectasis). In both conditions pneumococci are present in the sputum, and we consider these diseases as different phases in the same syndrome—pneumococcic bronchial obstruction.

frequent, if lobar bronchial occlusion is its immediate cause, considering the wide prevalence of bronchitis with sputum infected with virulent pneumococci. For it is known that the proportion of cases of lobar pneumonia to cases of acute bronchitis is less than the proportion of cases of postoperative atelectasis and postoperative pneumonia to cases occurring after abdominal or thoracic operations. The answer is that postoperative cases may have any or all of the contributory factors mentioned working to favor the production of pneumococcic atelectasis. In lobar pneumonia these factors have not been at hand, and this is why the incidence of pneumonia in acute bronchitis is relatively small. For this reason, when lobar pneumonia occurs spontaneously or following acute bronchitis, some unusual factors have been at play to cause bronchial obstruction, and these to our mind are the high virulence of the organism, the extreme (fibrinous) viscidity of the exudate which was initially able to occlude a lobar bronchus, and the allergic edema of the bronchial mucosa. Consequently, when "lobar pneumonia" ensues, the toxicity of the patient exceeds that of the patient with postoperative atelectasis or pneumonia. To the objection that there are no premonitory signs or preliminary bronchitis in lobar pneumonia the answer may be given that in postoperative atelectasis or postoperative pneumonia, also, there are no premonitory signs or symptoms; the disease starts within from twelve to twenty-four hours after a sterile operation whether done under local, spinal or general anesthesia. In other words there need not be an apparent preliminary cold or bronchitis; but it cannot be denied that postoperative pulmonary complications as well as medical lobar pneumonia occur relatively more frequently when a preliminary cold or bronchitis has existed. Austrian went so far as to say that if in lobar pneumonia a preliminary bronchitis has not been found it is because this condition has not been looked for. The facility with which, in a common cold, the nasal mucosa becomes so edematous as to obstruct breathing completely suggests at once that inflammatory or allergic edema of the bronchial mucosa can be an important contributory factor in complete obstruction of a lobar bronchus in pneumonia. Brown noted marked bronchial edema in atelectasis. In lobar pneumonia, after the initial bronchial occlusion with exudate, a pneumococcic invasion of the parenchyma occurs concomitant with the absorption of air and development of atelectasis. With the fibrinization and coagulation of the exudate, the infection may be considered as "fixed" below an obstruction, in an environment with little or no oxygen. We have previously shown (1929 [*b*]), that growth of pneumococci is markedly enhanced by moderately decreased oxygen tension in the medium. The experimental groundwork for this concept will be presented under "Experimental Data," and elaborated under "Comment." Groups 6 and 7 are of unusual interest in that they constitute the first reported

instances of experimental production of lobar pneumonia with human pneumonic sputum.

EXPERIMENTAL DATA

The experiments were carried out on dogs weighing from 10 to 12 Kg. Before bronchial manipulation of whatever nature, the animal was anesthetized with sodium amytal (sodium iso-amyl-ethyl-barbiturate), 55 mg. per kilogram being given intraperitoneally. Reference to table 1 will show the seven types of experiments that were done.

TABLE 1.—*Experimental Data*

Experiment	Agent	Procedure	Pathologic Condition Produced	Clinical Toxicity	Outcome	Reference to Figures in Text
1	Sterile balloon	Lobar bronchus obstructed 16-24 hr. with balloon	Atelectasis	Little or none	Recovery; re-aeration of lung	1
2	Sterile balloon	Lobar bronchus obstructed more than 24 hr. with balloon	Atelectasis plus serous exudate plus acute exudative lobar pneumonitis; if prolonged, necrosis in lung and purulent pleurisy; histologically, extreme diffuse exudation of pus cells with areas of necrosis	Mild to severe, depending on duration of obstruction	Recovery if removed within a few days; fatal if prolonged	1
3	Pneumococcus culture of low or moderate virulence	2 cc. of broth containing the sediment from a centrifugated amount of 18 hr. broth culture (1 cc. per Kg. of the dog's body weight) sprayed into right or left main bronchus	No bronchitis or mild bronchitis or pneumonitis with haziness over affected area in roentgenogram, with moderate variable shift of mediastinum and heart, and elevation of diaphragm; in other cases pneumococcic atelectasis (lobar pneumonia) with classic roentgen signs—monolobar types of disease frequent; nonresolution and pleurisy possible	None to moderate	Usually recovery if no complications arose, with gradual return of heart and mediastinum to normal position and re-aeration of lung	2 (A, B, C and D); 3 (A, B and C); 4, 5 and 6
4	Pneumococcus culture of high virulence	Same as in experiment 3	Acute pneumococcic atelectasis (lobar pneumonia); slight serous pleural effusion containing pneumococci; positive blood culture; histologic appearances of lung identical with those in human pneumonia	High	Usually fatal	7 and 8
5	Pneumococcus culture of moderate virulence plus obstructing balloon	Tip of balloon dipped in concentrated culture and then used in obstruction of lobar bronchus	Same as in experiment 4	High	Usually fatal	9
6	Human pneumonic sputum containing pneumococci of low or moderate virulence	5-6 cc. instilled into right main bronchus	None or mild bronchitis or pneumonitis or pneumococcic atelectasis	None to moderate	Recovery	10 and 11 (A, B, C and D)
7	Human sputum containing pneumococci of high virulence	5-6 cc. instilled into right main bronchus	Acute pneumococcic atelectasis (lobar pneumonia) with slight pleural effusion (serous); histologic appearance of lung identical with those in human pneumonia	High	Fatal	12 and 13

(Three hundred and ten dogs were used for the experiments of groups 1, 2, 3, 4 and 5, already described in previous publications.)

GROUP 1.—Our sterile obstructing balloon was placed in the left or right bronchus, inflated and left in for from sixteen to twenty-four hours. During this period atelectasis ensued with slight fever, an increased rate of respiration, cough and typical roentgenographic signs. On removal of the balloon, gradual re-aeration in from sixteen to

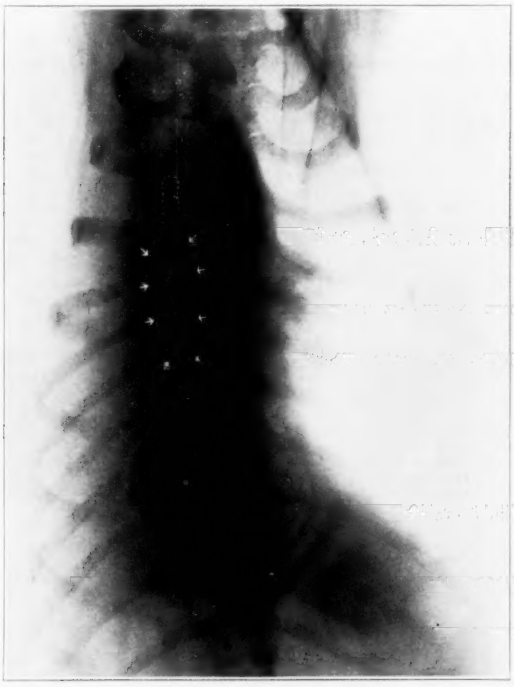

Fig. 1 (dog 47).—A roentgenogram taken twenty-four hours after obstruction of the right main bronchus with a special balloon; complete right massive atelectasis is seen. If obstruction is prolonged for from three to ten days, acute exudative pneumonitis, pulmonary necrosis, abscess, purulent pleurisy and death may ensue.

twenty-four hours was noted by roentgenogram, accompanied by considerable "dry coughing." There was little or no clinical toxicity (fig. 1).

GROUP 2.—The "obstructing balloon" was left in over twenty-four hours. The pathologic changes produced depended on the duration of obstruction and varied from a serous alveolar exudate to one with more

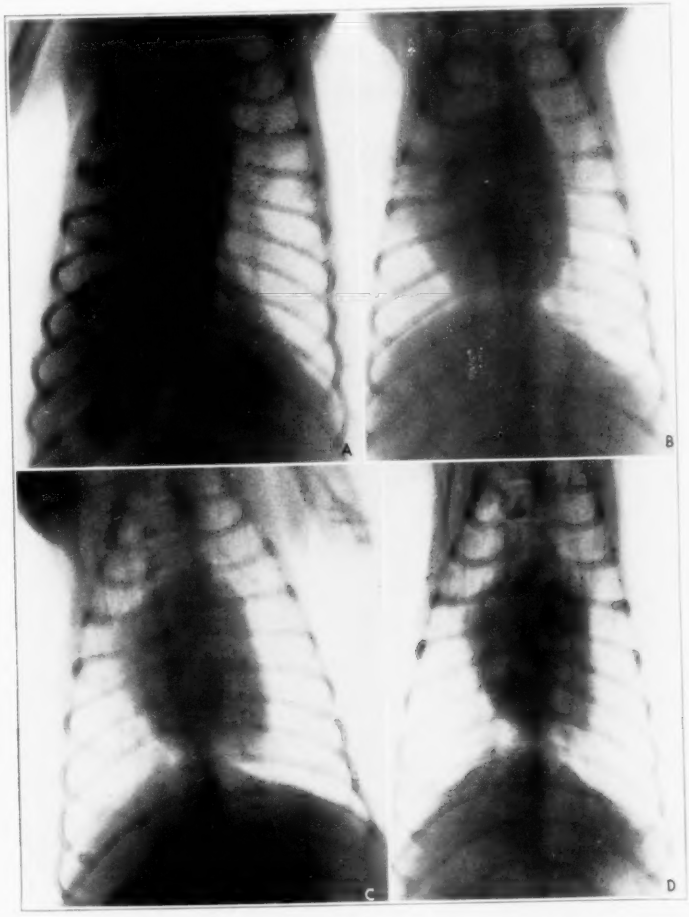

Fig. 2 (dog C45).—The spontaneous cure of lobar pneumonia (pneumococcic atelectasis) is illustrated. *A* shows the lung twenty-four hours after insufflation of 6 cc. of an 18 hour old broth culture of Pneumococcus, type I, into the right main bronchus; complete lobar pneumonia (pneumococcic atelectasis) has occurred. *B*, taken seventy-two hours after insufflation of culture, shows that the heart is on its way back to the left. The right lower lobe is clear; the right middle and upper lobes are still hazy. *C*, taken ninety-six hours after inoculation, shows the lung almost clear. *D*, taken five days later, shows the lungs clear and the heart back on the left.

or less exudation of polymorphonuclear cells into the alveoli and bronchiolar obstruction with this exudate. At a later stage acute, purulent pneumonitis was produced, with extensive exudation of polymorphonuclear cells into the alveoli and areas of pulmonary necrosis. At this stage there was also diffuse, purulent pleurisy. Grossly, the lungs were diffusely gray and consolidated and sank in water. Cut sections exuded

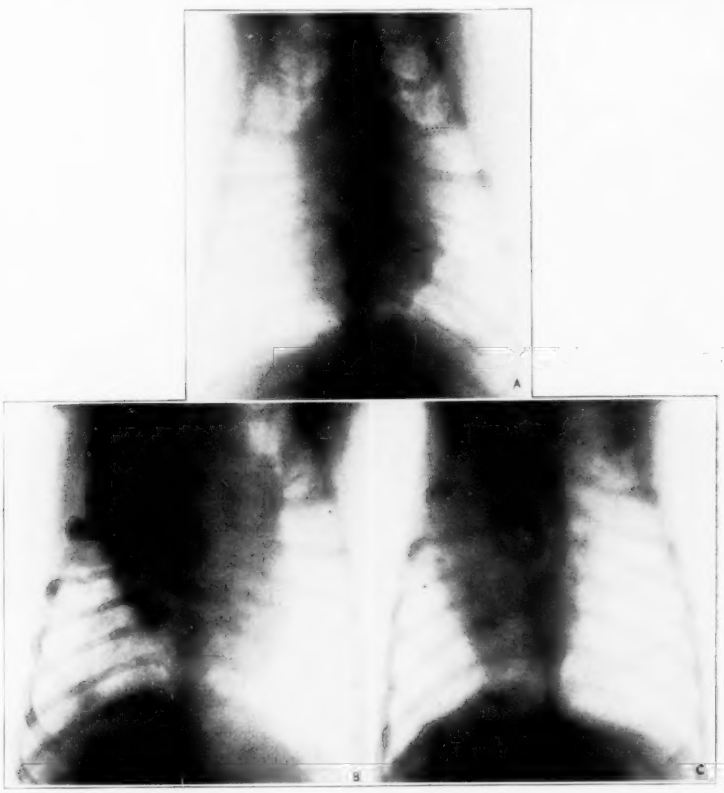

Fig. 3 (dog 741).—The figure illustrates an "unresolved" pneumonia of the right upper lobe resulting in pulmonary necrosis and abscess. *A* is the control film before insufflation of pneumococcus culture into the lung. *B*, taken three days after insufflation of 2 cc. (the concentrate of 14 cc.) of pneumococcus culture into the right main bronchus, shows the right lower lobe hazy and the right upper lobe definitely involved. *C*, taken thirteen days after insufflation, shows the right upper lobe still involved ("unresolved pneumonia"). The animal died on this day.

a dirty gray, purulent material from the bronchioles and alveoli. The animals generally succumbed to such obstruction if it was continued

for more than from three to ten days, with severe general toxic symptoms. On the other hand, removal of the obstructing balloon before this length of time as a rule resulted in recovery.

Group 3.—From 1 to 1.5 cc. of a culture of Pneumococcus, type I, of low or moderate virulence was given per kilogram of weight. This culture was a broth culture prepared from a pneumococcus not recently "passed" through the peritoneum of a mouse to augment its virulence. The calculated volume of culture, from 18 to 20 hours old, was centrifugated, the sediment suspended in from 1.5 to 2 cc. of broth and sprayed into the right or left main bronchus of the dog by means of a bronchoscope. Generally little or no toxicity was evidenced, with moderate rise

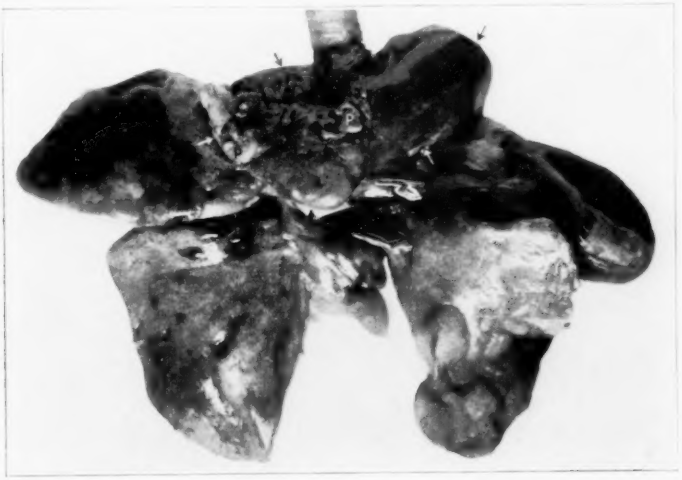

Fig. 4 (dog 741).—*A* is the abscess in the "unresolved" pneumonic right upper lobe; *P-P'* are areas where this lobe was adherent to the parietal pleura. The entire right upper lobe was markedly shrunken and liver-like. (The right upper lobe is indicated by arrows.)

of temperature and leukocytosis and little or moderate cough. The roentgenograms twenty-four hours after insufflation of the culture were negative or showed slight or moderate haziness over the affected lobes. In most instances, a moderate variable displacement of the heart and mediastinum to, and elevation of the diaphragm on, the affected side were noted. In a small proportion of cases a typical picture of atelectasis of low or moderate clinical toxicity was produced. In this group we obtained a greater proportion of monolobar involvement. Complete recovery was the rule, but in a few instances "nonresolution" with

a typical pathologic picture of lobar pneumonia was produced (figs. 2 *A*, *B*, *C* and *D*, 3 *A*, *B* and *C*, 4, 5 and 6).

Group 4.—A culture of a highly virulent pneumococcus was used, the broth culture being prepared from a strain just "passed" through a mouse. Practically a single pneumococcus, when intraperitoneally injected, was sufficient to kill a mouse. An amount of an 18 to 20 hour old culture equivalent to from 1 to 1.5 cc. per kilogram of weight was centrifugated and the sediment was suspended in from 1.5 to 2 cc. of broth and insufflated into the right or left main bronchus of the dog. Within from eighteen to twenty-four hours the animals

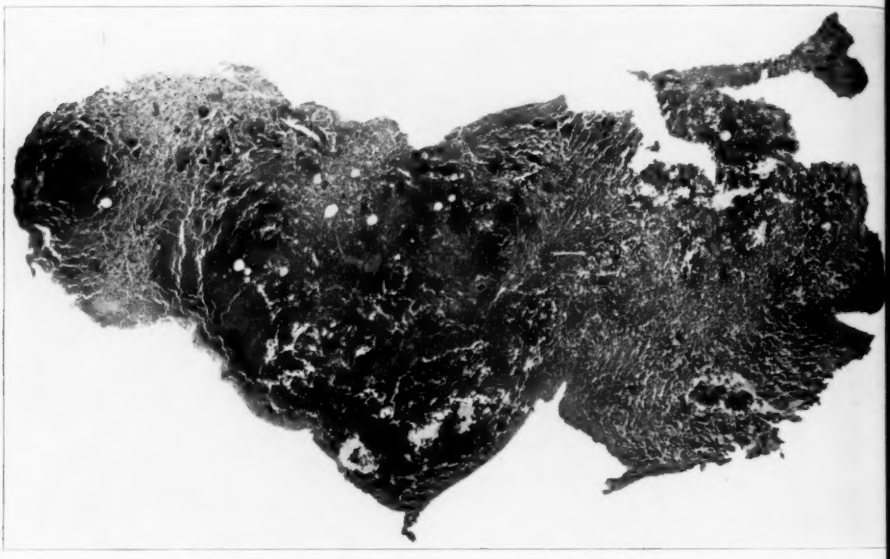

Fig. 5 (dog 741).—A low power photomicrograph through the abscess of the right upper lobe.

were very toxic or moribund, with marked leukopenia and a relative excess of polymorphonuclears (from 500 to 2,000 white blood cells; from 95 to 98 per cent polymorphonuclears), also subnormal temperature, dyspnea and rapid, shallow breathing. Blood cultures were positive in the majority of cases. The roentgenograms showed a classic atelectasis, i. e., a marked deviation of the heart and mediastinum to, and an elevation of the diaphragm on, the affected side. At postmortem examination, the affected lobes were indistinguishable by appearance alone from the atelectatic lobes in simple bronchial obstruction of twenty-four hours' duration. The lobar bronchi were

practically always occluded with a dirty, serosanguineous fluid which was more or less frothy and moderately thin. They sank in water, were uniformly deeply bluish red, and were smaller than the normal lobes when the trachea was clamped previous to opening the chest, and a little more edematous to touch than the atelectatic lobes in simple bronchial obstruction. In animals dying within from twenty-four to

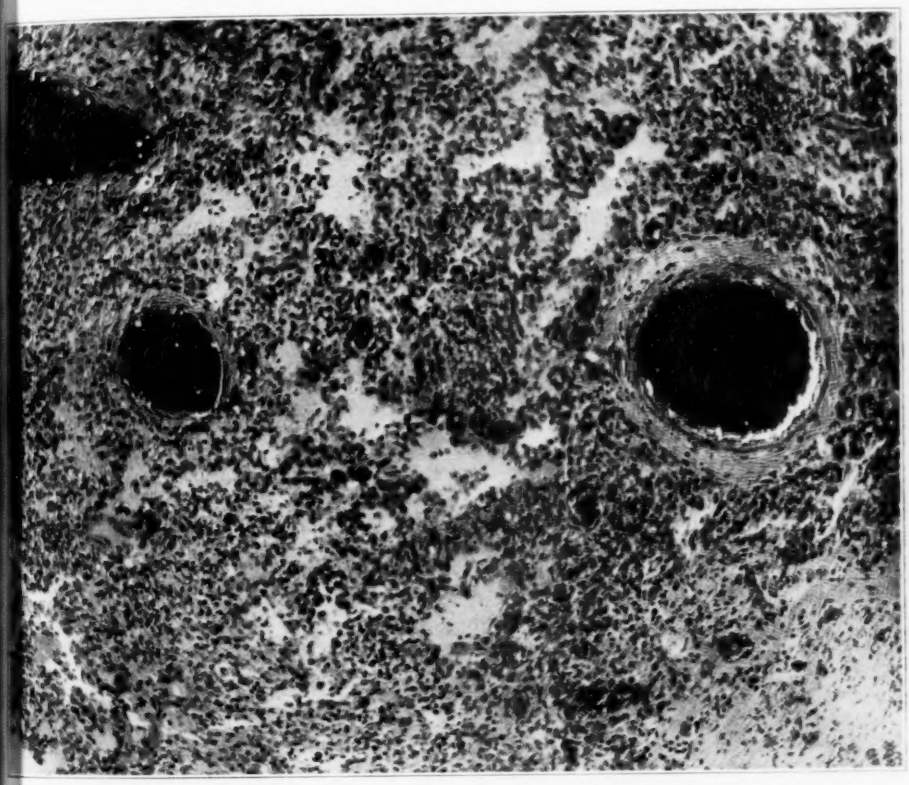

Fig. 6 (dog 741).—A high-power photomicrograph of the "unresolved" right upper lobe. This section is characteristic of the rest of the lobe. Note the dilated precapillary arterioles and the exudation of serum and leukocytes into the alveoli.

thirty-six hours after injection, the affected lobes were rather friable, cut sections exuding a moderately thick, dirty gray, serosanguineous material from the bronchioles. Animals dying after three days showed the diffusely irregular pinkish-gray mottling of early gray hepatization, when the bronchiolar and alveolar exudates were more

frankly gray and purulent. Microscopically, the picture shown in the sections was practically identical with that of human lobar pneumonia (sections examined by Dr. Douglas Symmers). Generally, however, the animals succumbed within forty-eight hours, with the lungs in the stage of "red hepatization" and with a slight serous pleural effusion containing pneumococci (figs. 7 and 8).

Group 5.—The end of the obstructing balloon was merely dipped in a culture of a pneumococcus of moderate virulence (concentrated by the

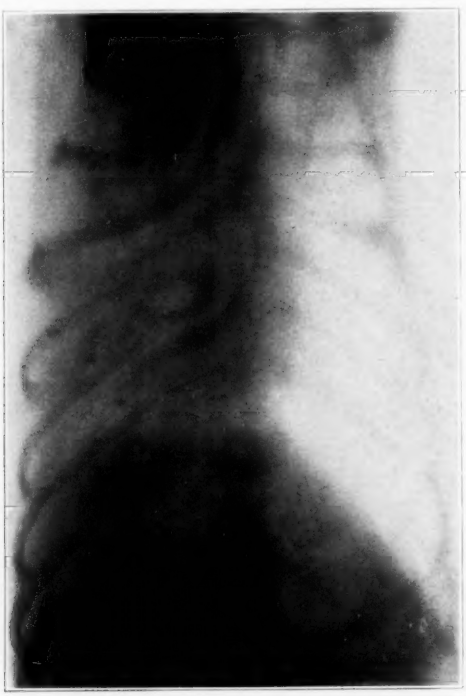

Fig. 7 (dog 734).—Twenty-four hours after insufflation of 11 cc. of pneumococcus culture (concentrated to 1.5 cc.) into the right main bronchus, a complete right lobar pneumonia (pneumococcic atelectasis) has occurred. This pneumonia was fatal in four days.

technic used for groups 3 and 4) and the balloon was introduced into the right or left bronchus of a dog (by the technic used for groups 1 and 2) and inflated to obstruct the bronchus completely for from eighteen to twenty-four hours. (Six dogs were used in this group.) Whether the balloon was removed or not, the animals succumbed

generally within from twenty-four to forty-eight hours after its introduction, and the findings and results were similar to those in group 4 (*q. v.*). In other words, a culture of moderate virulence was by this method able to produce a clinically high toxic picture (heart's blood and pleural exudate positive for pneumococci) and marked pathologic results. The infection appeared to have been "fixed" in the lung by

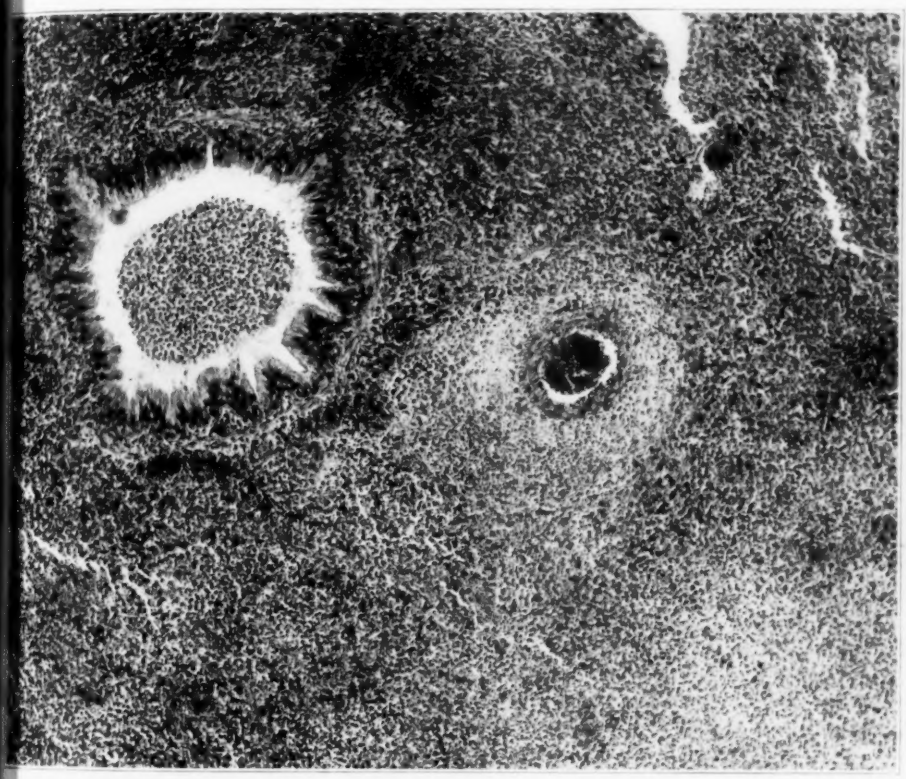

Fig. 8 (dog 734).—A high power photomicrograph of the right upper lobe.

the obstruction balloon, so that removal of the latter did not influence the fatal outcome. While the air was being absorbed, the infection traveled deep into the lymphatics and parenchyma and gave toxicity comparable to that of group 4. Another factor must be considered to account for the severity of symptoms and signs, namely, the enhancement of growth of pneumococci, which we have previously shown occurs in vitro with cultivation under reduced oxygen tension. Judged by

clinical symptoms, the virulence of the infection was raised by mechanical obstruction above the infection (fig. 9).

Group 6.—To our knowledge we are the first to have experimentally produced atelectasis or lobar pneumonia with human pneumonic sputum (dogs 639 and 640; weight, 8 Kg.).

Here fresh sputum from pneumonic patients with little evidence of toxicity was used. Six cubic centimeters of sputum freshly obtained was

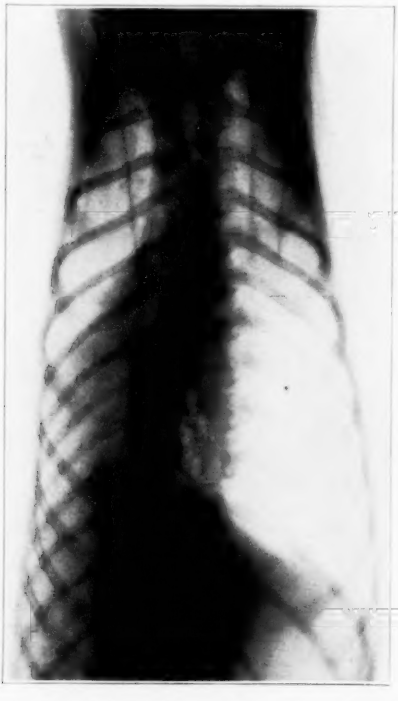

Fig. 9 (dog 38).—Twenty-four hours after obstruction of the right main bronchus with our special balloon, which was first dipped into an 18 hour old (ten times concentrated) culture of pneumococcus, the right lower and middle lobes were involved. This animal died with a rapidly fatal pneumococcic atelectasis (lobar pneumonia) and bacteremia.

instilled through the bronchoscope into the right or left main bronchus of each dog (previously anesthetized). After twenty-four hours or more, few or no clinical symptoms or toxicity had been produced. A mild cough, bronchitis or a slight haziness in the roentgen ray pictures with moderately variable degrees of deviation of the heart and mediastinum to, and elevation of the diaphragm on, the affected side were

noted. In one group, in which sputum of viscosity 90 was used, only a cough and moderate elevation of temperature were produced, with no other characteristic signs (dogs 649 to 650). Occasionally a typical atelectasis was produced (figs. 10 and 11 *A, B, C* and *D*), which resolved and gradually returned to a normal roentgen aspect. This type of atelectasis is directly comparable with that produced experimentally by Lee, Ravdin, Tucker and Pendergrass, using sputum from a patient with postoperative atelectasis, which they instilled into the bronchus of

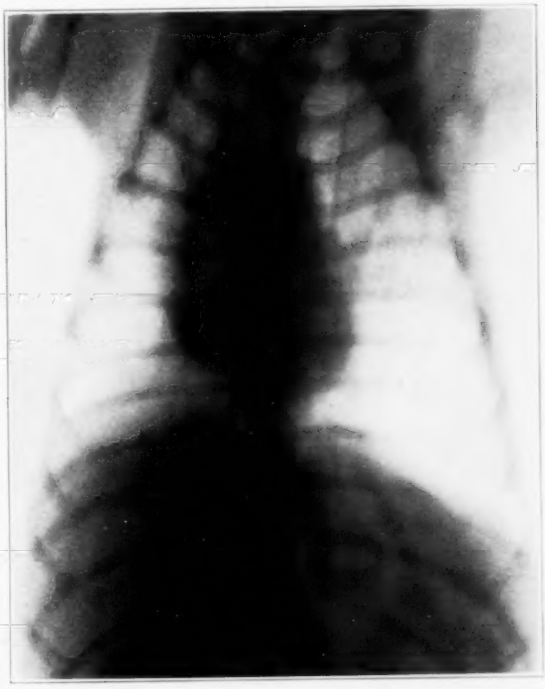

Fig. 10 (dog 639).—A roentgenogram illustrating the experimental production of lobar pneumonia (pneumococcic atelectasis) with human pneumonic sputum, with spontaneous recovery. This x-ray picture was taken twenty-four hours after the instillation into the right lower bronchus of 6 cc. of sputum from a patient suffering from lobar pneumonia whose blood culture was negative. The right lower lobe is hazy, and the right diaphragm, elevated.

a dog that had been submitted to morphine narcosis, laparotomy and tightly constricting abdominal bandaging. It will be recalled that all postoperative atelectatic sputums contain pneumococci, including the sputum which these authors used. The history of the patient whose sputum was used in group 6 follows:

J. O., aged 29, a white man, was admitted on Feb. 9, 1931, to Bellevue Hospital, in the service of Dr. Eugene F. DuBois. He had had a cough since February 2, which became productive with rusty sputum on February 7. On February 8, the day before admission, he had had chills, fever and pain in the right side of the chest and had vomited. On admission on February 9, physical examination showed involvement of the right upper lobe alone. His temperature was 101 F.; pulse rate, 110; respirations, 26. The white blood cell count was 16,400, with 92 per cent

Fig. 11 (dog 639).—*A*, taken two days after instillation of sputum, shows a very definite involvement of the right lower lobe (lobar pneumococcic atelectasis) with marked dextrocardia. *B*, taken three days after instillation of human pneumonic sputum into the right main bronchus, shows a slight clearing of the lower lobe and partial return of the heart to the left. *C*, taken five days after instillation of sputum, shows the lung practically normal and the heart almost entirely back in its normal position. *D*, taken six days after instillation of sputum, shows the lung normal and the heart in normal position.

polymorphonuclears. A blood culture was negative. On February 10, his temperature rose to 103 F.; the pulse rate was 120; the respirations, 24, with profuse coughing up of rusty sputum containing pneumococci of group I. The next day the temperature declined sharply to 100 F. (pulse rate, 100; respirations, 20), and his cough was slight and hardly productive. The temperature never rose above 100 F. from this point on and gradually declined to normal. He was discharged on Feb. 24, 1931.

Sputum for the experiment was obtained on Feb. 10, 1931, two days after the onset of the disease. Its viscosity was 10.

Fig. 12 (dog 627).—Twenty-four hours after instillation of 10 cc. of sputum from a pneumonic patient with a positive blood culture, this animal succumbed to complete right lobar pneumonia (pneumococcic atelectasis). The x-ray picture was taken after death.

Group 7.—In this group (dogs 627 and 628; weight, 12 Kg.) 10 cc. of freshly obtained sputum from a highly toxic patient with a positive blood culture was instilled through the bronchoscope into the right main bronchus of each dog (previously anesthetized). The animals were moribund within twenty-four hours, with the classic roentgen signs of pneumococcic atelectasis, and died within forty-eight hours.

Fig. 13 (dog 627).—A photomicrograph of the pneumonic lung.

The lungs were in the state of red hepatization, deeply reddish blue, and indistinguishable in appearance from atelectatic lungs. Grossly and microscopically, they had all the characteristics of the lungs of group 4 and of human pneumonic lungs in the stage of red hepatization. The pleural cavity contained a small amount of serous fluid (figs. 12 and 13). The history of the patient whose sputum was used for this group follows:

Fig. 14.—Photograph of a human pneumonic lung showing complete bronchial obstruction by a cast (courtesy of Dr. Norbert Enzer, Mount Sinai Hospital, Milwaukee). The blood culture was positive for pneumococcus, type I.

F. R., aged 40, a white man, was admitted on Jan. 19, 1931, to Bellevue Hospital, in the service of Dr. Eugene F. DuBois. He gave a history of a previous cold. Twenty-four hours before admission he had had a chill with pain over the fifth and third ribs on the right side. On admission, his sputum was "bloody." His temperature was 104 F.; his pulse rate was 120; his respirations, 26. Physical examination showed involvement of all the lobes on the right side. The white blood cell count was 14,000, with 90 per cent polymorphonuclears. A blood culture taken on January 22 was positive for Pneumococcus, group I. The sputum was likewise positive for group I. A blood culture made on January 24 was nega-

Fig. 13 (dog 627).—A photomicrograph of the pneumonic lung.

tive. His temperature ranged between 102 and 103 F. from January 20 to 23, when it declined to 100 and rose to 102 on the same day. On January 25, his temperature fell to 100 F. (pulse rate, 90; respiration rate, 18), gradually declining to normal. On February 2, a left sternoclavicular arthritis developed, which spontaneously cleared. By February 20, his lungs were clear, and he was discharged on Feb. 24, 1931.

Sputum for the experiment was obtained on Jan. 20, 1931, two days after the onset of the disease. Its viscosity was 30, and the p_H, 7.4.

COMMENT

Reference has been made to the extreme viscosity of the pneumonic sputum. The deleterious qualities of pneumonic exudate reside not only in its viscosity, but also in its content of virulent pneumococci and the presence of fibrin, the coagulability of which is a serious drawback to drainage of the finer bronchioles and parenchyma. The sputum of atelectasis and that of pneumonia cannot be rigidly classified, for the former also has a content of pneumococci, and the change from one to the other could occur by slow degrees with increasing virulence of pneumococcic content. At any rate, sputum coughed up is not necessarily an index of the type of bronchial mucus or exudate occluding a lobe of the lung. Sputum coughed up may represent merely an overflow from the bronchus of the affected lobe. It would be difficult, for example, to conceive of the hemorrhagic, rusty sputum in pneumonia as coming entirely from the parenchyma proper when the lung is filled with coagulated fibrinous exudate; moreover, the actual quantity of sputum coughed up is very small, as compared with the volume of exudate of an affected lobe as seen post mortem. Should pneumonic sputum have a high content of mucoid material, its origin from the alveoli proper is precluded, for mucous glands exist only in bronchi of a diameter of 1 mm. or more. An overflow from the mouth of a lobar bronchus is perfectly compatible with its still remaining perfectly occluded with mucus and exudate and the parenchyma filled with a fibrinous exudate.

We have produced "full-blown" and rapidly fatal experimental lobar pneumonia by instillation of 10 cc. of only moderately viscid sputum (viscosity 30) obtained on the second day of disease from a toxic pneumonic patient with a positive blood culture; this sputum was instilled into the main bronchus of an anesthetized dog. On the other hand, with other sputum of viscosity 90 or more, as compared with water obtained from a less toxic patient, only evanescent pneumonitis with early symptoms of atelectasis (a moderate shift of the heart and mediastinum and an elevation of the diaphragm) was obtained. The ease of experimental production of the signs of atelectasis appears, therefore, to be related not only to viscosity but also to the virulence of the pneumococcic content. We have shown that 1 cc. of a ten times concentrated broth culture of a virulent strain of pneumococci is suffi-

cient to cause pneumococcic atelectasis when sprayed into the bronchus of a dog anesthetized with amytal. The sputum of atelectasis invariably contains pneumococci, and Lee, Ravdin, Tucker and Pendergrass were able to reproduce the signs of atelectasis by instilling "atelectasis sputum" into the bronchus of a dog with the aid of abdominal incision, constricting abdominal bandages and morphinization. Their experimental production of atelectasis is comparable to that in our group 6, in which we produced atoxic atelectasis by human pneumonic sputum containing pneumococci of low or moderate virulence. Furthermore, we believe that the experimental cases in which we produced mildly toxic states, together with typical shift of heart and mediastinum and elevation of the diaphragm, by bronchial injection of a culture of a moderately virulent pneumococcus or by moderately virulent human pneumonic sputum stand in more direct analogy to clinical cases of postoperative atelectasis which, because of the growth of pneumococci in the bronchial secretions or alveolar exudate, border on or merge into a toxic state and are commonly known as cases of "postoperative pneumonia." The only distinction, if any, that clinically can be made between postoperative atelectasis and postoperative pneumonia is the greater toxicity of the patient, for the physical and roentgen signs are identical in both instances. Only too often the clinician cannot be sure whether he is dealing with pneumonia complicating atelectasis or with atelectasis complicating pneumonia.

Standing as an extreme phase in the syndrome of pneumococcic bronchial obstruction and as a condition analogous to severe postoperative pneumonia or medical lobar pneumonia is the experimental lobar pneumonia (pneumococcic atelectasis) which we produced by insufflation of a culture of a highly virulent pneumococcus or by instillation of 10 cc. of human pneumonic sputum from a toxic patient into the bronchi of dogs. These animals were extremely sick or moribund, with roentgen signs of atelectasis, marked toxic leukopenia, polymorphonuclear cytosis, subnormal temperatures and positive blood cultures. In this regard it is noteworthy that elevation of the diaphragm on the diseased side and variable degrees of mediastinal shift to the same side are often noted in human lobar pneumonia. Never in uncomplicated pneumonia is the mediastinum or the heart deviated away from the diseased side, indicating that the pneumonic lobe is never larger than the corresponding healthy one, as we first showed (1929).

It should be remembered that an infection in the lung, as elsewhere, which is toxic for one patient may be less toxic for another, and this consideration further decreases the possibility of arbitrarily marking off the phases of pneumococcic bronchial obstruction by clean-cut dividing lines.

That the phenomenon of pneumococcic atelectasis of a lobe may occur with relatively thin exudate might be accounted for by the dele-

terious effect of the latter on the ciliated epithelium, by the greatly diminished effectiveness of cough in an enfeebled toxic patient, or by both, and by the edema of the bronchial mucosa. The initial period of complete obstruction of a lobar bronchus, whether by thick or by thin exudate or by mucopus, need not be long before a generalized bronchial and alveolar outpouring of serum, polymorphonuclear cells and fibrin occurs; once this takes place, re-aeration of the myriads of alveoli and bronchi becomes very difficult.

The objection has been raised that in lobar pneumonia or even postoperative pneumonia, no "plug" is found in a lobar bronchus. "Plug" should not be taken to mean a corklike type of occlusion at one point in the bronchial tree. It refers to a variable column or mass of fluid or semifluid, mucoid or fibrinous secretion or exudate. It is not expected, therefore, when a bronchus is cut open, to find a more or less firm obstruction. The cutting of the bronchus disrupts and dissipates the obstructing column along the wall of the bronchus. Furthermore, the rapid autolysis of exudate after death accounts for the absence of firm exudate in, and obstructing, a large bronchus; the smaller bronchi remain obstructed. This also accounts for the frothy fluid found in the bronchus post mortem which was not present during life.

It is evident that in postoperative atelectasis re-aeration can and does usually occur coincident with profuse expectoration and cough. Since it is obviously impossible for an airless lung to empty itself of exudate by the compressive phase of cough, this must be accomplished by the gradual ingress of air between the obstructing material and the bronchial wall, so that there is some force below the obstruction to expel an occluding column or mass of exudate. The greater the re-aeration the more effective does cough become; and it is obviously the deep inspiratory phase of deep cough which accomplishes this re-aeration and gradual expulsion of foreign material. This process of "resolution" would seem reasonably to hold for moderate or severe types of lobar pneumonia as well. The lung in which postoperative atelectasis or postoperative pneumonia is present may take from ten to fourteen days or more to "resolve" and re-aerate, and the lung in which an abortive or short-lived pneumonia is present may "resolve" and re-aerate in a few days. On the other hand, the lung in which a postoperative atelectasis or a postoperative pneumonia is present can "resolve" and re-aerate within a few days, and the lobe in which a lobar pneumonia is active may take from ten to fourteen days or more to "resolve" and re-aerate. In both instances—postoperative atelectasis or pneumonia and lobar pneumonia—the marked clinical relief sets in long before the roentgen and clinical aspects of the disease indicate complete re-aeration and long before the coughing up of mucopus or exudate has ceased.

In all three conditions the amount of edema in the lung or of fibrin in the exudate may be an important factor in determining the rapidity of "resolution," drainage and re-aeration. In those types of lobar pneumonia with considerable fibrinous exudate, it is likely that liquefaction is greatly aided by the two proteolytic enzymes (Opie and Lord; Jobling and Strouse; Ascoli and Bezzola; Bittorf) liberated by the white cells in the exudate, after the exudation into the lung of antitryptic substances in the serum has ceased. One of the enzymes is effective in neutral medium and the other in slightly acid medium. Reference to table 2 will show the marked decrease in viscosity and p_H value that occurred after incubating pneumonic sputum for from

TABLE 2.—*Viscosity and Hydrogen Ion Values of Pneumonia Sputum*

Sputum	Comment	Group of Pneumococcus	Viscosity (Compared with Water)	p_H Plain	p_H After Bubbling CO_2 for 15 Minutes*	p_H After Bubbling Air for 15 Minutes
1. Jan. 14, 1931	.....	1	96	7.65	6.80	7.65
	After 24 hr. in incubator.....	...	1	5.64	5.45	5.55
2. Jan. 10, 1931	.....	1	"Very viscid"	7.47	6.57	7.47
	After 24 hr. on ice..	...	"Very viscid"	....	7.16	7.48
	After 24 hr. in incubator.....	...	"Flows readily"	....	5.92	6.22
3. Jan. 20, 1931	.....	1	30	7.40	6.55	
	After adding 1/15 its volume of dilute mercuric chloride solution against bacteria and 24 hr. in incubator.....	...	2	6.95	6.025	

* Carbon dioxide bubbled before incubation only.

eighteen to twenty-four hours at body temperature. The decrease in viscosity of one specimen of pneumonic sputum from 96 to 1 and the decrease in p_H value are interesting. A marked decrease in p_H value is a factor unfavorable to the growth of pneumococci.

The "crisis" of pneumonia may indicate sufficient liquefaction of the intrapulmonary exudate to allow beginning ingress of air into the finer bronchi and alveoli and beginning pouring out of the lung of its liquefied matter—the volume of sputum is increased after crisis, as a rule. It is, of course, commonly accepted that a variable quantity of alveolar exudate is absorbed from the lung after crisis. The beginning re-aeration and drainage could give clinical relief in the same manner that the opening of even a relatively small focus of pus or an abscess elsewhere in the body can give relief. With the liquefaction of exudate by enzymes and drainage of the lung, the virulence of those microbes

which have survived destruction may be greatly reduced by the unfavorable environment. This concept is in keeping with the principles of drainage of other organs in the body, and can be applied to postoperative atelectasis, postoperative pneumonia and lobar pneumonia. In the lung, as with other organs, besides the local focus of infection there are general symptoms, which in pneumococcic atelectasis consist of toxicity and bacteremia. To combat the disease and overcome the general symptoms one must at least attack the focus of infection.

Those who would deny the mechanism of pulmonary drainage and recovery from pneumonia which has been described may invoke the idea of a formation of antibodies which overcome the infection. But, so far as we know, the existence of antibodies at the time of crisis is by no means constant. If such antibodies are always present, it is difficult to explain the susceptibility to pneumonia which a previous attack may confer. What is more difficult to understand is the resolution of one lobe and shortly afterward a new involvement of another lobe. We have previously shown the marked impairment of capillary circulation both in atelectatic and in pneumonic lungs, and it is difficult to see how sufficient antibodies could effectively enter the alveolar exudate. There is no doubt that the biochemistry of pneumonic exudate needs further study so that there may be an established basis on which to treat the disease directly at its focus.

To ignore the interrelation of postoperative atelectasis, postoperative pneumonia and lobar pneumonia as types in the syndrome of pneumococcic bronchial obstruction is to close our eyes to the possibility of rational therapy. Contrariwise, keeping this view in mind, we can begin to see the reason for therapeutic hyperventilation with carbon dioxide, which is now more commonly employed in postoperative routine, in carbon monoxide asphyxia and in lobar pneumonia. The aim of carbon dioxide therapy is to overcome the acapnia (carbon dioxide deficiency) caused by rapid, shallow breathing, to maintain or open the airways of the lung and to exert an antagonistic biochemical effect on the growth of pneumococci. On the latter point, further data will be published in a forthcoming paper.

As with other pathologic states, the prevention is better than the cure. The lung is normally one of the best drained organs of the body, but once bronchial obstruction occurs, it is apt to be the most poorly drained. Under normal conditions, it maintains its health in spite of the inhalation of countless microbes, irritating gases and particles of matter because its airways are kept open by various means: by the constant vigil of the cough reflex, by adequate ventilation, by the constant washing out of mucus, and by the ciliary epithelium and possibly by the rhythmic peristaltic action of bronchi—all of which are means to keep the bronchi

open and prevent obstruction and absorption of air with the ever-present danger of bacterial growth. Other microbes, when concerned with bronchial obstruction, may cause pyogenic or putrid abscess or gangrene.

In cases of pneumococcic bronchitis, repeated inhalations of mixtures of oxygen and carbon dioxide certainly constitute an excellent preventive and often curative treatment. When chill, elevation of temperature, toxic general symptoms, increased dyspnea and cyanosis, which indicates bronchial obstruction, are present, nothing is more efficient than bronchoscopic reestablishment of the patency of the bronchi. This measure, when early applied, gives gratifying results. If we can induce internists to give a fair trial to this physiologically, experimentally and clinically rational and innocuous method, instead of allowing the disease to establish itself unhampered, we shall have accomplished a great deal. Our general conception of the rôle of bronchial obstruction in pulmonary disease is offered in the accompanying outline.

Bronchitis without bronchial obstruction = simple bronchitis

Bronchial obstruction

- Small bronchi or bronchioles
  - "Plug"* infected with pneumococci of low virulence = patchy atelectasis
  - "Plug" infected with highly virulent pneumococci or other microbes = bronchopneumonia
  - "Plug" infected with pyogenic organisms or anerobes = abscess or gangrene
- Bronchi of larger size
  - "Plug" infected with microbes of low virulence = lobar or massive atelectasis
  - "Plug" infected with highly virulent pneumococci = lobar or massive pneumonia
  - "Plug" infected with pyogenic organisms or anerobes = abscess or gangrene

* "Plug" refers to a variable column or mass of fluid or semifluid, mucoid or fibrinous secretion or exudate, and must not be taken to mean a corklike type of occlusion at one point in the bronchial tree.

SUMMARY AND CONCLUSIONS

The part played by bronchial occlusion in the pathogenesis of neonatal or postnatal atelectasis and pneumonia, postoperative atelectasis and pneumonia and lobar pneumonia has been pointed out. The agent of such obstruction may vary, but when the obstruction is complete, the end-result is the same—atelectasis. Outside of amniotic fluid or fetal epithelial cells in the new-born infant, foreign bodies, intrabronchial or extrabronchial tumors and lesions of the bronchial walls, the agent that most frequently causes bronchial occlusion and the resulting varieties of atelectasis is viscid sputum or exudate.

In lobar or massive postoperative atelectasis, pneumococci, especially group IV, are always present in the sputum. Similarly, lobar pneumonia is almost always associated with pneumococci. This incidence is explicable on the basis of the type of exudate which pneumococci produce in both instances—an exudate viscid enough to occlude a lobar bronchus and cause air absorption and atelectasis. In contrast to lobar atelectasis and lobar pneumonia, lobular atelectasis and lobular pneumonia are usually associated with other organisms, such as staphylococci, streptococci, Bacillus influenzae, etc. In nine cases of lobar pneumonia which were treated by bronchoscopy, the bronchus to the affected lobe was always found occluded with exudate. This conception offers a clear explanation of the "lobar" distribution of "lobar pneumonia."

By physical and roentgen signs or even by the gross pathologic appearances it may be impossible to distinguish postoperative atelectasis, postoperative pneumonia and lobar pneumonia. In a general way, the clinical toxicity is proportionate to the virulence of the pneumococcus concerned. In lobar pneumonia there is a more marked degree of pneumococcic cellulitis and alveolar exudation, factors which may make the underlying or basic atelectasis less evident in the gross pathologic and roentgen pictures.

Experimentally, instillation of human pneumonic sputum into the bronchi of animals produced either evanescent symptoms or the clinical and roentgen pictures of lobar or massive atelectasis. Some of the latter cases went on to spontaneous recovery; others terminated fatally. Presumably the virulence of the pneumococcus concerned was the factor determining the outcome. The toxic or fatal conditions in this group were clinically comparable to lobar pneumonia, whereas the less toxic ones in which recovery occurred were clinically comparable to lobar or massive atelectasis. In man, the same difficulties are encountered, and the differential diagnosis between postoperative atelectasis, postoperative pneumonia and lobar pneumonia usually rests largely on the factor of toxicity, when the other symptoms and signs run closely parallel.

The purest types of atelectasis are represented by the condition of the normal fetal lung before respiration is instituted. After respiration has started, the inspiration of amniotic fluid or fetal epithelial cells (dermal) may cause a sterile atelectasis which when infection with micro-organisms has occurred can progress to lobar pneumonia.

The clinical toxicity of postoperative atelectasis, postoperative pneumonia and lobar pneumonia depends on the virulence of the pneumococcus concerned in the exudate causing bronchial obstruction. Absorption of alveolar gases and atelectasis occur with a spread of the infection toward the alveoli. The degree of shift of the heart and mediastinum and that of elevation of the diaphragm are inversely proportional to the amount of alveolar exudate, and this accounts for the less marked roent-

gen signs of atelectasis in lobar pneumonia, although there are cases in which the roentgen signs in pneumonia are the classic signs of atelectasis, especially in children.

In the light of the theory given, if the occluding agent has been a septic foreign body or a piece of tonsillar tissue, atelectasis can be followed by anaerobic infection with necrosis, gangrene or anaerobic abscess.

The symptom complex in pneumococcic bronchial obstruction is variable. What are apparently different clinical conditions should be grouped as different phases of one and the same syndrome. The underlying or basic pathologic condition is atelectasis, but the clinical aspect depends on the size of the occluded part of the lung, the duration of the bronchial occlusion, the type and virulence of the infecting micro-organism, the character and the amount of the alveolar exudate and the complications which may arise. Keeping the etiologic identity of these clinical conditions, which have usually been considered basically different, in mind, one is better equipped to recognize and to treat properly the disease complex as a definite but variable entity—the syndrome of pneumococcic bronchial obstruction.

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BOOK REVIEWS

Outline of Preventive Medicine for Medical Practitioners and Students. Prepared under the auspices of the Committee on Public Health Relations, New York Academy of Medicine. Twenty-four contributors. Editorial Committee: Frederic E. Sondern, Charles Gordon Heyd and E. H. L. Corwin. Second edition. Price, $5. Pp. XVII + 462. New York: Paul B. Hoeber, Inc., 1932.

The first edition of this book was published in 1929. It was reviewed in *The Journal of the American Medical Association* (**93**:1585 [Nov. 16] 1929). The volume was composed mainly of a series of articles by specialists written in an attempt to advise and instruct the general practitioner in matters concerning preventive medicine. Certain of the chapters were criticized as being fragmentary and vague or hurried. In general, however, the book received favorable comment. It appeared to have a praiseworthy aim and, in spite of various shortcomings, to give promise of being serviceable to the medical profession by directing attention to the fundamental obligation of the physician to aid in the prevention of disease.

That the book has fulfilled a useful purpose is evidenced by the publication of a second edition within such a short space of time. The second edition is sixty-four pages longer than the first and contains four new chapters. One chapter on industrial disease which appeared in the first edition has been deleted.

The body and the appearance of the book are much as when it first appeared, except for occasional new paragraphs which have been added here and there to amplify or to modernize certain topics. Undulant fever, for example, is now considered as being largely a preventable disorder through pasteurization of infected milk, and the preventable aspects of tularemia and psittacosis are discussed. Rabies receives considerably more space than it was given at first. No mention is made in either edition of the importance of cinchophen and allied substances in causing a preventable form of acute yellow atrophy of the liver.

Dr. Bronson Crothers' name is misspelled as Crowthers in both printings. A typographic error of this sort, occurring twice, arouses the suspicion of possible carelessness for the manner in which the references that are quoted have been verified.

The chapters that have been added deal with preclinical medicine and with hygiene, the prevention of oral disease, medical service in industry and the relation of the private physician to the health authorities. Of these, the first describes how physicians can sensibly instruct their patients who are not ill in the art of keeping well; the second stresses the importance of dental care and mouth hygiene; the third tells of the work of the present-day industrial physician, and the fourth summarizes the scope of the modern public health department, emphasizing the point of view that the various activities of public health authorities do not invade the field of the private practitioner but, rather, stimulate an increasing demand for his services.

On the whole, the book continues to make pleasant reading. The editors, in introducing it, remark that there evidently is a need for a book of this character. They suggest that subsequent editions describing important new conquests of disease will be published from time to time. Each succeeding volume of the series should be of increasing value, interest and completeness.

Lehrbuch der inneren Medizin. By G. von Bergmann, F. Stroebe, R. Doerr, H. Eppinger and others. In 2 volumes. Price, 49.80 marks. Pp. 1,650, with 276 illustrations. Berlin: Julius Springer, 1931.

In accordance with the more modern trend, this textbook is written by a group of authors. A number of the writers, it will be noted, are among the outstanding

clinicians of Germany. As one would suspect, this work is detailed and is written in scholarly fashion. It is probably to be recommended more as a reference book than as a textbook.

Volume I is divided as follows: (1) The introduction by Dr. R. Siebech is a discourse on the art of medicine and also includes outlines for history taking and physical examination; (2) Infectious Diseases, by Dr. R. Doerr and Dr. R. Staehelin; (3) Diseases of the Cardiovascular System and Mediastinum, by Dr. P. Morawitz; (4) Diseases of the Respiratory System, by Dr. S. J. Thannhauser; (5) Diseases of the Digestive Tract, by Dr. W. Stepp; (6) Diseases of the Liver and Biliary Tract, by Dr. G. v. Bergmann with Dr. F. Stroebe.

Volume II is divided as follows: (1) Diseases of the Urinary Tract, by Dr. H. Strausz; (2) Metabolic Disorders, by Dr. L. Lichtwitz; (3) Diseases of the Organs of Internal Secretion, by Dr. Hans Eppinger; (4) Diseases of the Blood and Blood Forming Organs, by Dr. A. Schittenhelm; (5) Diseases of the Muscles, Bones and Joints, by Dr. S. J. Thannhauser; (6) Diseases of the Nervous System, by Dr. F. Hiller; (7) The Neuroses, by Dr. R. Siebech; (8) Toxicology, by Dr. P. Morawitz; (9) Diseases Due to Physical Agents, by Dr. S. Katsch; (10) Injuries Due to Radioactive Rays, by Dr. R. Schittenhelm; (11) General Therapeutic Measures, by Dr. L. Lichtwitz.

This work is more extensive than our most popular medical textbooks, but the general plan in the presentation of the various diseases is similar. Rare diseases are printed in small type. Considerable emphasis has been placed on pathology and physiology. The material is for the most part original and is based on the experiences of the authors. Numerous references are made to the literature throughout the text, and a bibliography appears at the end of each section. However, there are few or no references to other than German literature. One of the fine features of this textbook is the abundance of illustrations. This is especially true in the sections on gastro-intestinal, cardiac and thoracic diseases. Here are used clear reproductions of the roentgenograms illustrating each of the diseases under discussion. The section on neurology contains numerous photographs and charts. Methods of treatment are those in use on the continent.

Teachers of medicine will find this book a valuable source of information.

Manipulative Surgery. By A. S. Blundell Bankart, M.A., M.Ch. (Cantab.), F.R.C.S. Price, 7 shillings, 6 pence. Pp. 162. London: Constable & Co., Ltd., 1932.

This is an unusual book, covering a subject which surgeons shun and of which most of them are wofully ignorant.

The introductory section deals with general subjects, such as anatomic considerations, sprains and adhesions, postural activity of muscles, chronic strain, joint subluxations, arthritis, the general principles of manipulation, anesthesias, the limitations of, and the results that can be expected from, manipulating various types of conditions.

The subsequent sections deal specifically with conditions involving the feet, the knees and hips and muscles and tendons in the lower extremities, spine and pelvis, and the fingers, hands and wrists, elbows and shoulders.

There are three outstanding chapters, which alone make reading this book profitable, those dealing with the foot, knee, spine and pelvis. The meaning, mechanism and treatment of "foot strain," as presented, will, I warrant, give most surgeons an entirely new aspect on this subject. The "derangements of the knee," particularly displaced semilunar cartilages and especially the pathology and treatment are clearly presented. Pains in the lower region of the back are differentiated, and indications for and methods of manipulation are prescribed, again a subject in which the average surgeon has limited knowledge.

The manipulation of joints properly requires a tremendous amount of experience and absolute confidence in one's own ability to do it. Most men would hesitate to apply as great a force to the joints as the author claims is necessary for good results, for fear of overdoing it and producing untoward results.

One connected with a large clinic, where opportunity for constant application of these principles is afforded, doubtless would find this book of much practical value. The average physician would change many of his ideas about these conditions of the joint, but would probably have limited opportunity to make use of the treatments prescribed.

A Handbook of Experimental Pathology. By George Wagoner, M.D., Associate in Pathology, and R. Philip Custer, M.D., Associate in Research Pathology, University of Pennsylvania, Philadelphia. Price, $4. Pp. 160, with 6 tables and 23 figures. Springfield, Ill.: Charles C. Thomas, 1932.

Prof. Edward B. Krumbhaar, in introducing this volume, aptly terms it a pioneer effort. The book purports to be a modest handbook of experimental pathology based on the course in this subject given to the second year students of medicine in the University of Pennsylvania Medical School. It appears to achieve its aim.

The first chapter deals with technic. In it is found a good description of how to care for the various kinds of animals that may be utilized in experimental work; how to house and feed them; metabolism cages and operating tables; anesthetics and their dosage and methods of use; ways for obtaining specimens, and, finally, a table of normal blood and blood chemical findings for the various species. This introductory chapter is written sanely and, above all, emphasizes the fact that to carry out acceptable animal experimentation the perfection of surgical care is essential.

The ensuing chapters describe standard methods for producing and studying a great many lesions of different kinds. A wide range of subjects is covered, including experiments dealing with general pathology, the special pathology of the various systems of the body, the vitamins and the phenomena of hypersensitivity. Thus there is condensed into the body of the book a description of how to reproduce in animals most of the important occurrences in man with which a beginning pathologist must become familiar.

A textbook of this sort is so interesting and timely that the authors are to be congratulated on having put it together. Medical schools other than its alma mater will be quick to appreciate its usefulness.

The Cardiac Output of Man in Health and Disease. By Arthur Grollman, Ph.D., M.D., Associate Professor of Physiology, Johns Hopkins University. Price, $4. Pp. 325. Springfield, Ill.: Charles C. Thomas, 1932.

As is suggested by the title, this monograph discusses cardiac output in a most comprehensive fashion. It includes a bibliography of 483 references.

A history of the early attempts to estimate cardiac output is followed by an account of the more important investigations that have led to the establishment of the direct and indirect methods for the determination now in use. Several indirect methods are compared in regard to their relative accuracy, and the advantages and disadvantages of each one are analyzed. The general principles and technical details of the acetylene method advocated by the author are described.

The effect of various physiologic factors which may influence cardiac output is emphasized. The section of the book relating to this matter is perhaps the most notable part of the volume, since the author establishes by his own method, in a series of carefully executed determinations, a set of normal values essential to the interpretation of results obtained under abnormal conditions. The effect on cardiac output of different drugs, including various endocrine gland extracts, and of certain diseases is dealt with, and, finally the author attempts to correlate cardiac output with other physiologic functions.

The entire study is presented in a succinct, lucid and stimulating fashion. Certainly it will interest clinicians as well as physiologists, particularly those clinicians who are devoting attention to the investigation of problems related to the circulatory system.